STUDIES IN BIOGENETIC ASPECTS OF PHENOL OXIDATION

Thesis submitted

by

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University of Glasgow

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Microanalyses are by Mr. J.M.L. Cameron and his staff.

CONTENTS

SUMMARY

Laudanosoline-4':6-dimethyl ether has been postulated as the phenolic precursor in the biogenesis of morphine alkaloids and aporphine alkaloids of the glaucine and corytuberine type.

A thirteen-step unambiguous synthesis of laudanosoline-4':6-dimethyl ether is described starting from isovanillin.

Oxidation of laudanosoline-4':6-dimethyl ether with alkaline potassium ferricyanide has been attempted under varying conditions of pH, concentration, phenol-oxidant ratio, reaction time, order of addition of the oxidant and phenol etc.. The results of these experiments are discussed in the light of the spectroscopic and paper chromatographic properties of the oxidation products. Several experiments have been carried out to resolve authentic mixtures of aporphines and laudanosine by paper chromatography and the knowledge gained in these experiments has been successfully employed in the resolution of products obtained by the oxidation of laudanosoline-4':6-dimethyl ether with alkaline ferricyanide. In a number of experiments the R_f values of certain components of the oxidation product point to the formation of aporphines.

An attempted synthesis of laudanosoline-4':6-diisopropyl ether, from papaverine via laudanosoline-3':7-dimethyl ether, the reported demethylation product of laudanosine, is described.

3-isoPropyl morphinone has been prepared from morphine and converted back into it.

SECTION I

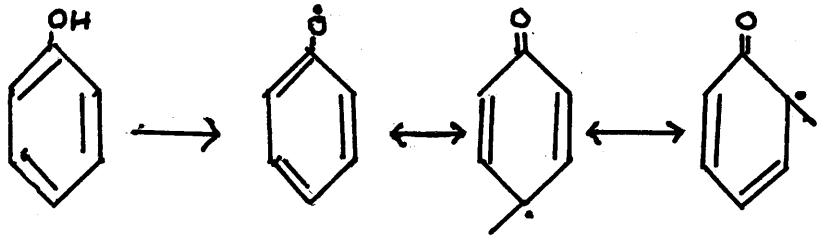
[References in this Section appear after each chapter]

INTRODUCTION

The oxidation of phenols has been studied for a very long time [1]*. The fundamental importance of this reaction in elucidating the chemistry of 'Free Radicals' [2], the practical importance of the use of phenols as retarders and inhibitors in the autoxidation and olefin polymerisation processes [3] and the biogenetic implications of the oxidative coupling of phenolic compounds [4] have more recently stimulated the interest of leading organic chemists in this field.

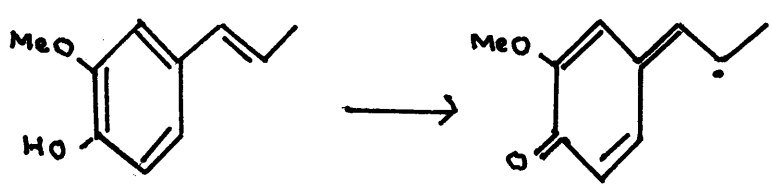
The oxidation of phenols or of phenolate anions by one electron transfer oxidising agents [5] yields phenol radicals which are stable, as compared with the rather transient alkyl radicals. This relative stability of phenol radicals is easily understood as the odd unpaired electron can spread by resonance over the ortho and para positions of the aromatic nucleus giving rise to the mesomeric forms, (I), (II), (III) etc., which were at one time thought to be mere tautomers [6].

Footnote* Numbers in square brackets refer to References.



I II III

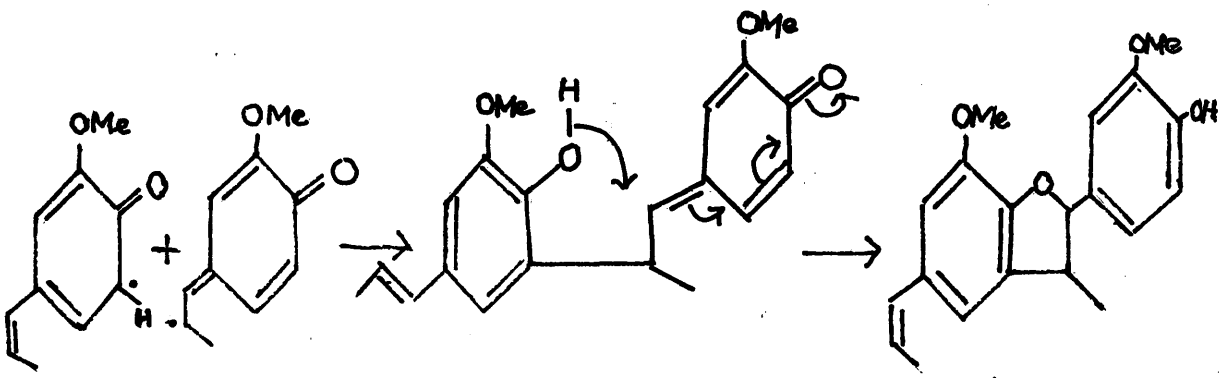
This resonance stabilisation can be extended still further in the case of radicals derived from phenols containing an unsaturated side chain in the ortho or para positions to the hydroxyl group so that the double bond of the side chain is in conjugation with the aromatic nucleus. Thus, isoeugenol (IV), for example, can give rise to still another mesomeric form of the phenol radical (V). The possibility of such a mesomeric radical, first suggested by Erdtman [7], was subsequently substantiated [8] during the dehydrogenation of ferulic acid to dehydrodiferulic acid (see Chapter II, page 77).



IV V

The formation of dehydrodiisoeugenol (VI) also probably involves the

coupling of one such radical with a normal radical, at an intermediate stage (see VII) [9].



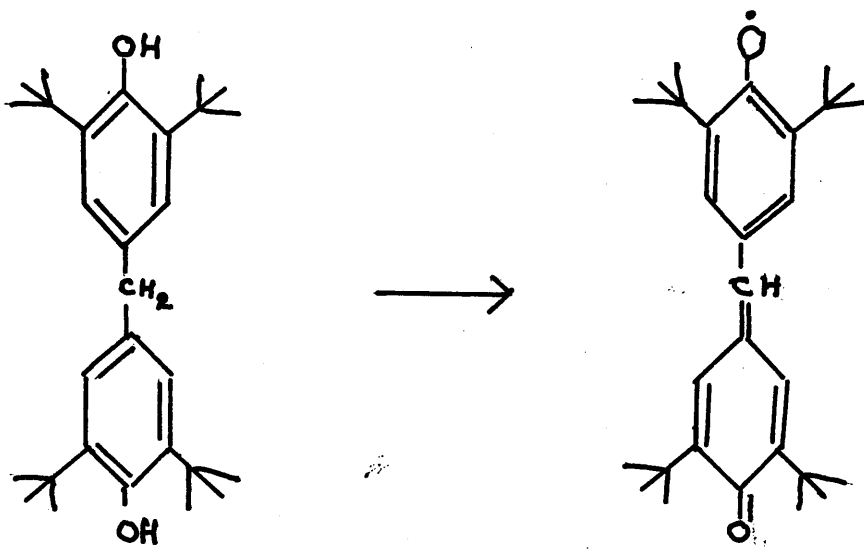
V VII VI

A large variety of oxidising agents has been employed, for example, ferric chloride, potassium ferricyanide, silver oxide, lead dioxide, lead tetraacetate, oxygen,hydrogen peroxide, persulphates, quinones, enzymic preparations, etc.. Electrolytic methods of oxidation have also been frequently used.

Pummerer and his collaborators [10], [11], [12] were the first to appreciate the importance of phenol radicals as intermediates in phenol oxidations but the first experimental proof for the actual existence of these radicals has been given only very recently [13], [14], [15], [16], [17]. These papers not only describe the isolation of stable, solid radicals from suitable phenols, but also include a detailed study of the chemical and physical properties of such radicals.

Thus, oxidation of 2:4:6-tritertiary butyl phenol (VIII; R'=R''=R''' = t - Bu; see Flow Sheet I p.6A), for example, affords, on oxidation, in quantitative yields an intense blue solid radical (IX; R' = R'' = R''' = t - Bu) which reacts with oxygen to yield the peroxide (X; R' = R'' = R''' = t - Bu). With chlorine or phenyl iodochloride this radical gives (XI; R' = R'' = R''' = t - Bu) and with bromine the corresponding bromo-compound (XII; R' = R'' = R''' = t - Bu). Nitrogen dioxide similarly furnishes the nitro-compound (XIV; R' = R'' = R''' = t - Bu) and so on. The oxygen uptake by (IX) is quantitative and can be used to determine the amount of (IX) present. The 2:4:6-tri-tert-butylphenoxy radical (IX; R' = R'' = R''' = t - Bu) could also be assayed by catalytic hydrogenation with platinum in acetic acid or by titration in benzene under an inert atmosphere with hydrazobenzene solution in benzene or by reaction with sodium iodide in acetic acid when the liberated iodine could be titrated against sodium thiosulphate. The continued oxidation of this stable phenoxy radical affords the quinone methide (XVII; R' = R''' = t - Bu) which adds alcohols furnishing the corresponding p-alkoxymethyl phenols (XVIII; R' = R''' = t - Bu) which give stable radicals on oxidation in the same way as the parent tri-tert.-butyl phenol (VIII; R'= R'' = R''' = t - Bu). The methide (XVII; R' = R''' = t - Bu) is reduced by lithium aluminium hydride to regenerate the

original phenol. Some of these properties of the 2:4:6-tri-tert.-butylphenoxy radical have been summarised in the Flow Sheet I, page 6A. Besides the extreme chemical reactivity of this radical referred to above, paramagnetism by virtue of the presence of an unpaired electron is also exhibited. The infra red spectrum of this radical shows characteristic absorption resembling a weak carbonyl absorption [14] (see Table I)p.6. Still another extremely stable phenoxy radical (XXXI) deep blue needles (from ethanol), m.p. 157.5°, has recently been reported to have been obtained by the alkaline ferricyanide oxidation of 4:4'-dihydroxy-3:5:3':5'-tetra-tert.-butyl diphenylmethane (XXX) [80]. The weak carbonyl absorption at 1572 cm^{-1}, the U.V. and magnetic properties of the radical are also described.

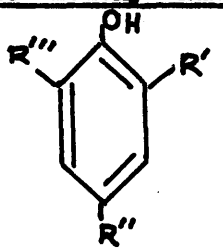


XXX XXXI

Similar behaviour is shown by the phenols (XIX) - (XXIX) (see Table I). The p-alkoxyphenoxy radicals, (XXV) for example, are incidentally considerably more stable than those from p-alkylphenols.

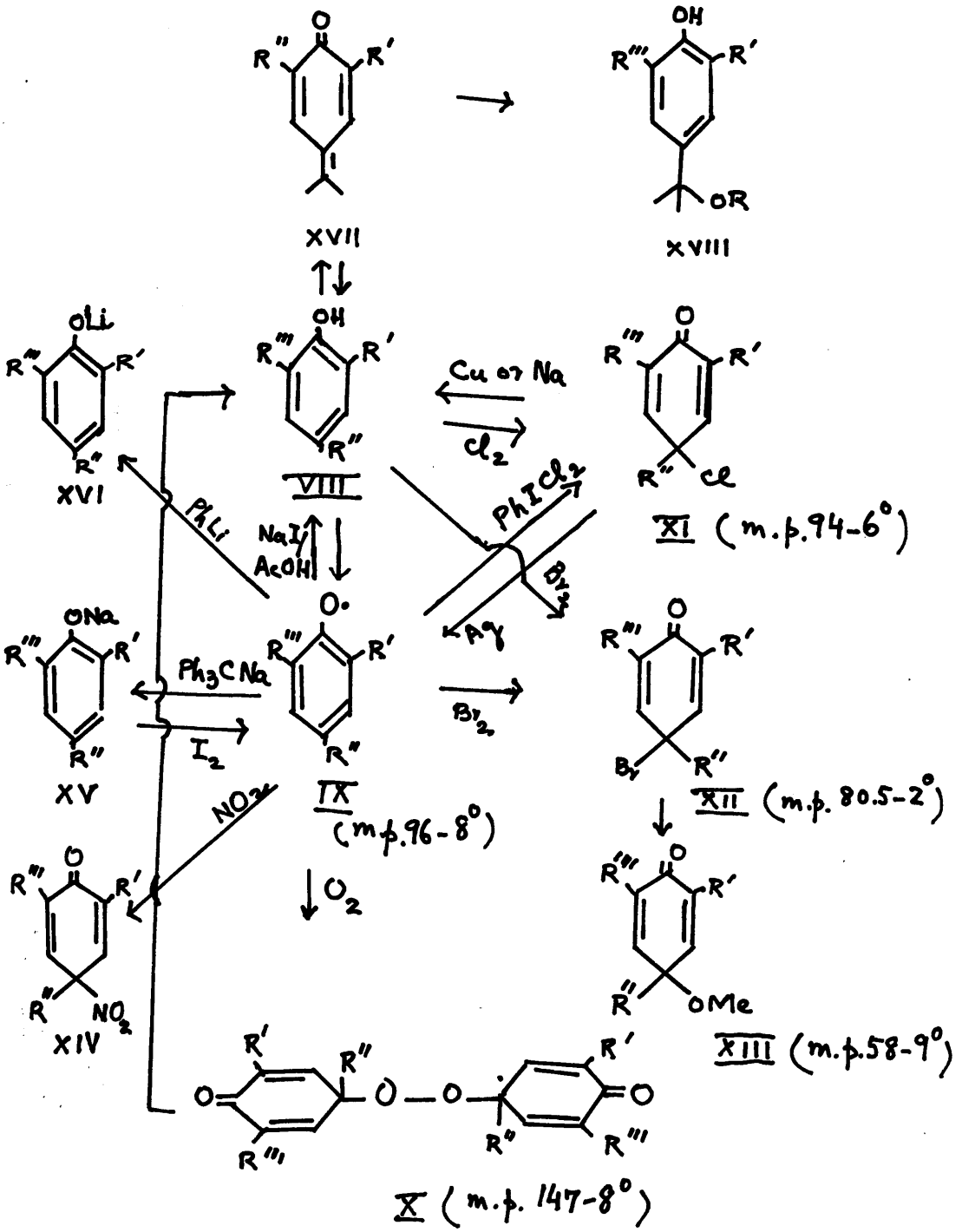
TABLE I

Stable Phenoxy Radicals

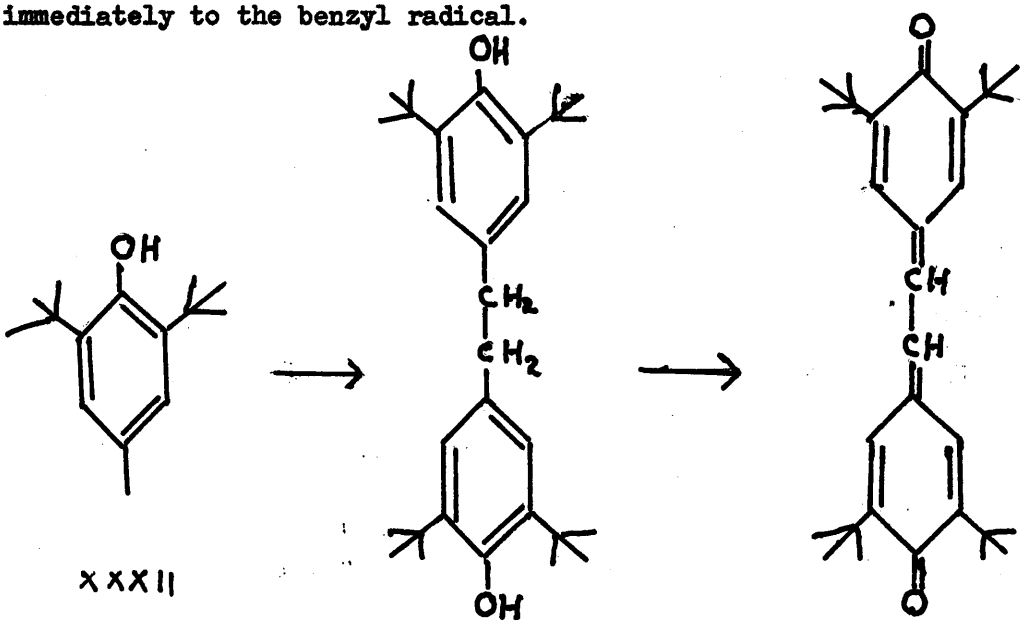


Phenol	R'	R''	R'''	Colour of Radical	Infrared Peaks cm^{-1}	References
VIII	t-Bu	t-Bu	t-Bu	Blue	1507 M 1573 S	
XIX	t-Am	t-Am	t-Am	Blue	1507 M	[18], [19]
XX	"	OMe	"	Red	1590 S 1509 M	[18]
XXI	"	O-Am(t)	"	Red	-	[18]
XXII	t-Bu	Me_2C(Me)-OMe	t-Bu	Blue	-	[18]
XXIII	"	Me_2C(Me)-OEt	"	Blue	-	[18]
XXIV	"	OMe	"	-	-	[18], [20]
XXV	"	OEt	"	Red	1590 S 1509 M	[18], [19]
XXVI	"	OBu(t)	"	Red	1590 S 1509 M	[18], [21]
XXVII	"	i-Pr	"			[22]
XXVIII	"	see-Bu	"			[22]
XXIX	"	t-Bu	OBu(t)			[21]

FLOW _ SHEET I

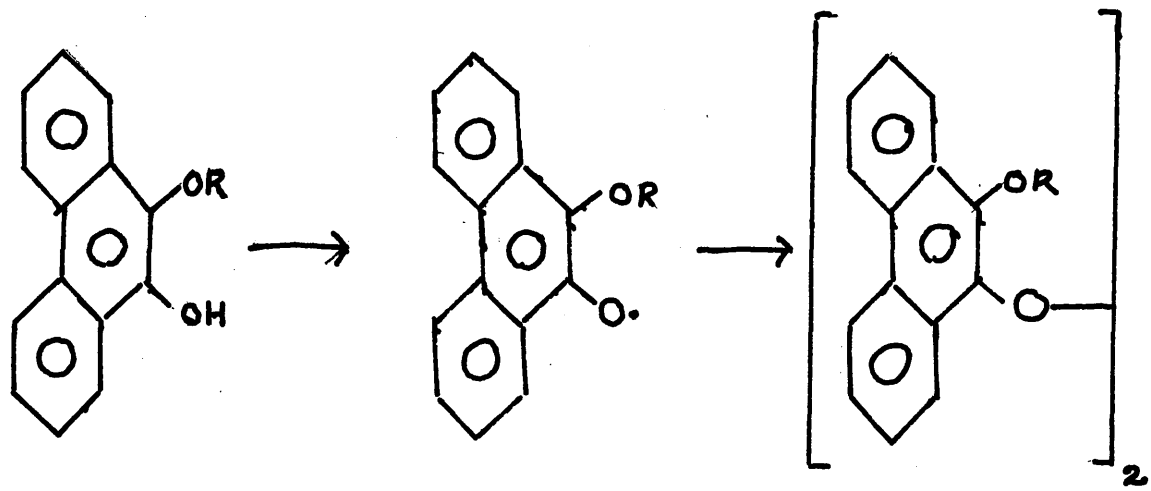

XVII
XVIII
XVI
VIII
XI (m.p. 94-6°)
XV
IX (m.p. 96-8°)
XII (m.p. 80.5-2°)
XIV
XIII (m.p. 58-9°)
X (m.p. 147-8°)
Cu or Na
Cl2
PhICl2
PhLi
NaI
AcOH
Ph3CNa
I2
Br2
Ag
NO2
O2

The extraordinary stability of these 2:4:6-trisubstituted phenol radicals is not difficult to understand because apart from their protection from coupling or attack on nucleus due to steric reasons, none of the substituents contain any α-hydrogen atom and consequently the formation of reactive methylene quinones is also prevented. When the ortho or para position of the phenols carries a methyl group, as in 2:6-di-tert.-butyl-4-methyl phenol (XXXII), the phenoxy radical rearranges to give two products (XXXIII) and (XXXIV) [19]. Quantitative measurements of these products confirm the stoichiometry and suggest that the phenoxy radical formed initially rearranges immediately to the benzyl radical.



XXXII XXXIII XXXIV

During their studies on the oxidation of phenanthrols [(XXXV); R = Me or Et)], Goldschmidt and co-workers [23] obtained colourless, crystalline dimers which were formulated as peroxides [(XXXVI; R = Me) and (XXXVI; R = Et)]. While these dimers were more stable in the solid form, they gradually dissociated in solution to form coloured radicals, presumably [(XXXVII; R = Me or R = Et)] till an equilibrium was reached.



XXXV XXXVII XXXVI

These equilibria were detected by changes in the apparent molecular weight, colour of the solutions which do not obey the Beer-Lambert law, and by criteria already referred to, like the extreme chemical reactivity towards radical trapping agents,

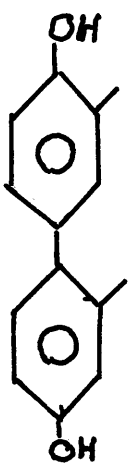
paramagnetic susceptibility, etc., [24]. Rummerer and his co-workers have also demonstrated the presence of similar equilibria between the dimers and intermediate radicals [10], [11], [12], [25], [26].

The oxidation of hydroquinones to quinones also involves phenol radicals (semiquinones) or the corresponding anions as essential intermediates which have essentially the same properties as the ordinary phenol radicals. The reversibility of the hydroquinone-quinone redox system enables the formation of these semiquinone intermediates to be detected with precision by electrochemical methods [27], [28], [29], [30], [31].

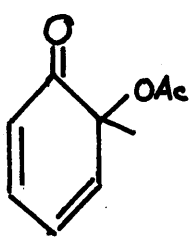
Thus we have fairly convincing evidence for the existence of phenol radicals as a molecular species.

However stable these phenol radicals may be, they are only relatively so and cannot remain indefinitely in that state, unless special precautions are taken. Even the so-called stable phenol radicals disproportionate slowly at as low a temperature as -200°C, and have a rather limited life period. These radicals must then find some way to be converted into stable molecular species and there are several ways by which this stabilisation can be brought about.
As already pointed out; they may be reduced back to give the parent

phenol [13], [14], [20], [23], [30], [31], or react with molecules like oxygen, halogens, etc., giving non-radical products. These radicals may undergo 'self-coupling' to furnish dimers and/or polymers. We shall return to this aspect later when it will be discussed in greater detail. Other reactions, notably substitutions ortho to the existing hydroxyl groups, may result from what are apparently slight variations of reaction conditions [32], [33], [34], [35], [36], [37]. For example, o-cresol, on oxidation with lead tetraacetate in benzene, yields 3:3'-dimethyl-4:4'-dihydroxydiphenyl (XXXVIII) but affords the acetoxy cyclohexadienone (XXXIX) on oxidation with lead tetraacetate in acetic acid [34], [36].



XXXVIII

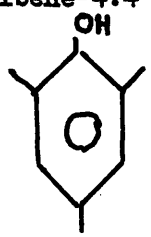


XXXIX

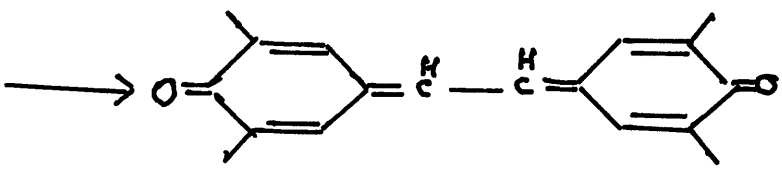
These variations in the 'type' of the products formed may be due to factors which may either stabilise a mesomeric form of the

phenoxy radical and permit dimerisation or enhance the possibility of acetoxylation and dienone formation. The formation of the acetoxy dienone in this particular case is presumably assisted by the propagation of acetate radicals in acetic acid. Other factors like the solvent effect, the proportion of the oxidising agent, the position and number of methyl substituents also determine the 'type' of product isolated, [34]. In many cases, however, these variations could be ascribed to the intervention of heterolytic oxidation processes.

The dismutation of phenol radicals or progressive removal of electrons from polyhydric phenols or certain alkyl phenols of suitable structure resulting in the formation of quinones, quinone methides or their di- or polymerisation products has already been indicated. Mesitol (XL), for example, affords on oxidation 3:5:3':5'-tetramethyl stilbene-4:4'-quinone (XLI) [38], [39], [32].



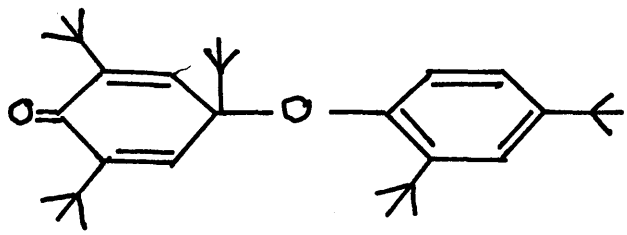
XL



XLI

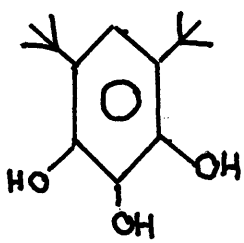
Disproportionation of phenol radicals has also been observed in certain cases. Cook et al. found, for example, 2:4:6-tri-tert.-butyphenol, isobutylene, and a substance formulated as (XLII) among the

disproportionation products of 2:4:6-tri-tert-butyl phenoxy radical (IX, R'=R''=R''' = t-Bu) [18].

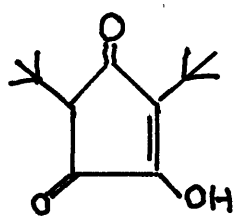


XLII

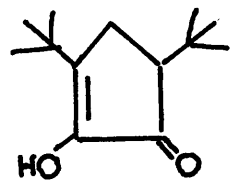
Ring 'fission', ring 'contraction' and ring 'expansion' are some of the other complications encountered during the oxidation of certain phenols. Thus the oxidation of 4:6-ditert.-butylpyrogallol (XLIII) afforded, on oxidation in alkaline media with air, among other products (XLIV) and (XLV) [40], [41].



XLIII

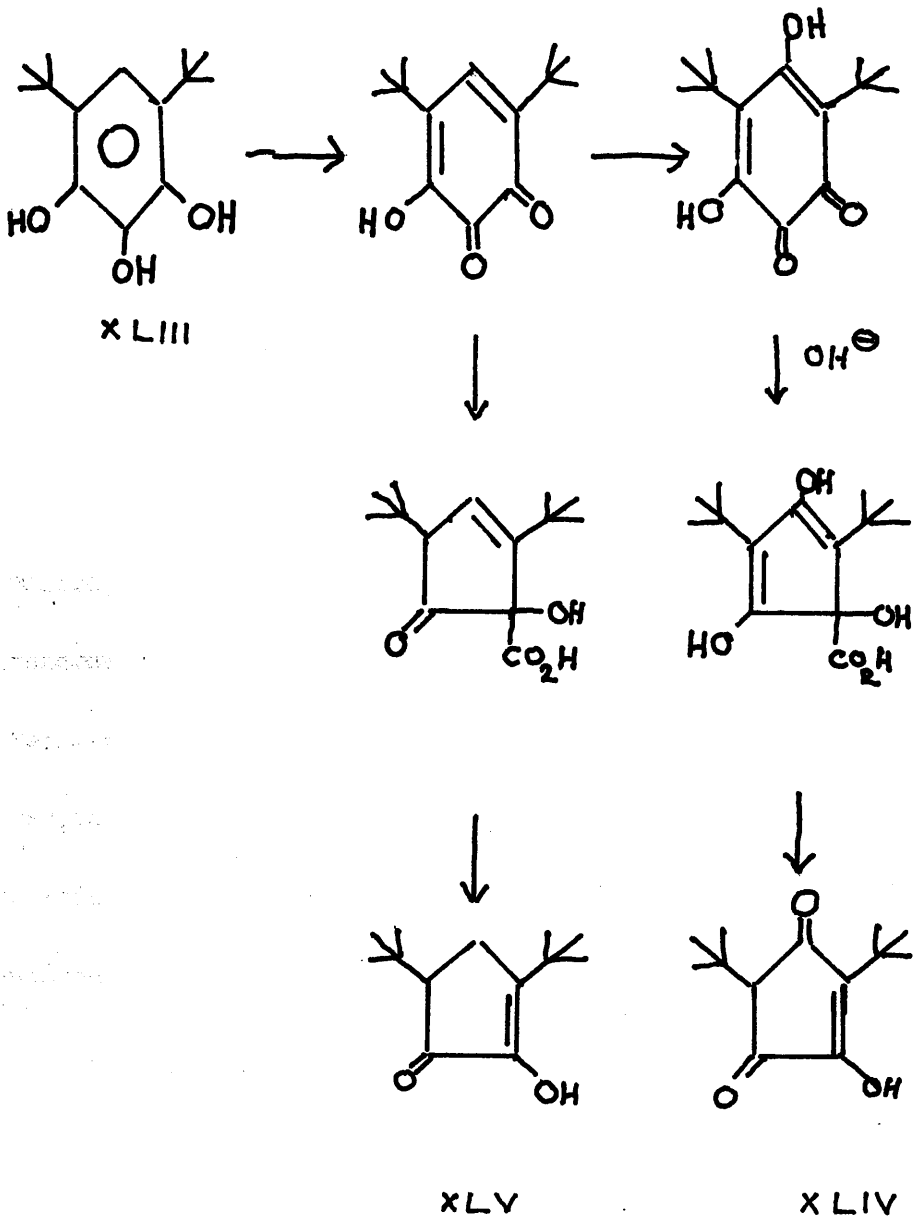


XLIV

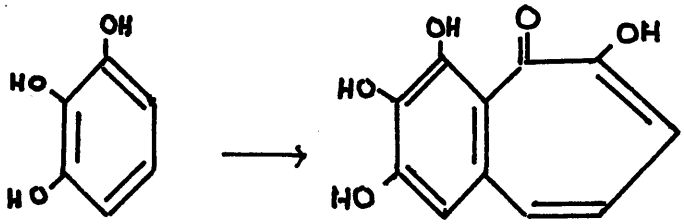


XLV

The mode of formation of (XLII) and (XLIII) is probably the one indicated below:



Purpurogallin (XLVI) [42], [43], [44], [45], [46] obtained from pyrogallol under phenol coupling conditions, represents a case of ring expansion although its exact mode of formation is not entirely understood as yet.



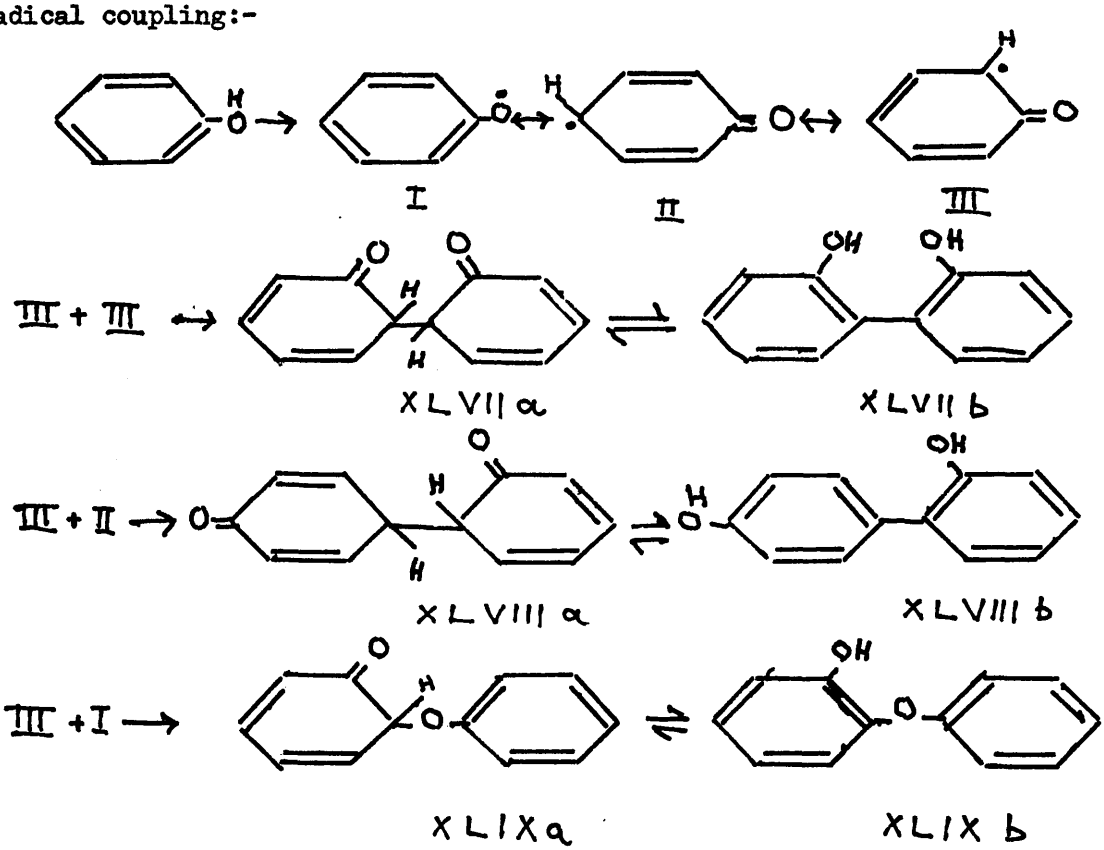
XLVI

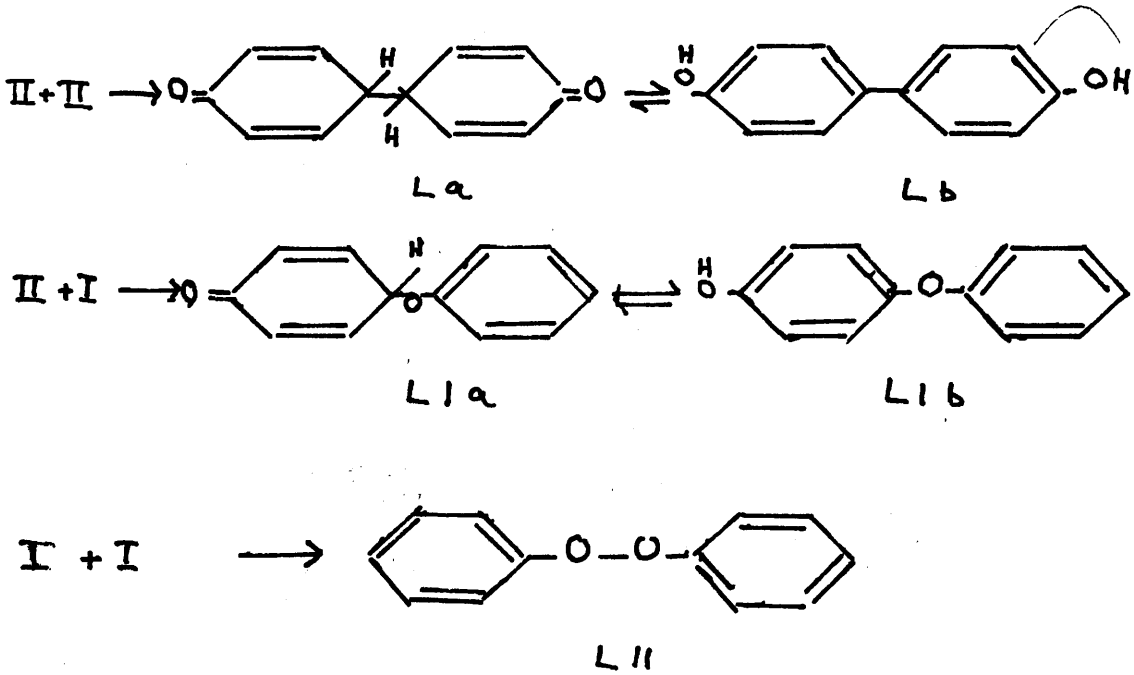
In short, phenol oxidation is a complex process and as a rule "large amounts of by products, generally ill-defined, are simultaneously formed due to hydroxylation, ring 'fission' or 'polymerisation'. In several cases, the presence of diphenyl or diphenyl ether linkages has been recognised in the amorphous reaction products. The large number of isomeric forms, due to restricted rotation, in which many polyphenyl derivatives can exist certainly contributes to the great complexity and unattractive nature of these products" [46].

Let us now return to examine in more detail the possibility of phenol radicals undergoing self-coupling and furnishing dimers and/or polymers, referred to already. This 'self-coupling', though by no means a major reaction of these radicals, as has been shown above, has particular bearing on the present work.

The 'self-coupling' of phenol radicals may involve 'carbon-

carbon', 'carbon-oxygen' and 'oxygen-oxygen' coupling. The 'carbon-carbon' coupling, which is the most important of all, could occur at ortho-ortho, ortho-para or para-para positions of the mesomeric aryloxy radicals once they are formed. The different structures of the products of such oxidation becomes fairly obvious from this wide variety of possible types of union. Some such possibilities are illustrated below for the simple instance of 'phenol' radical coupling:-



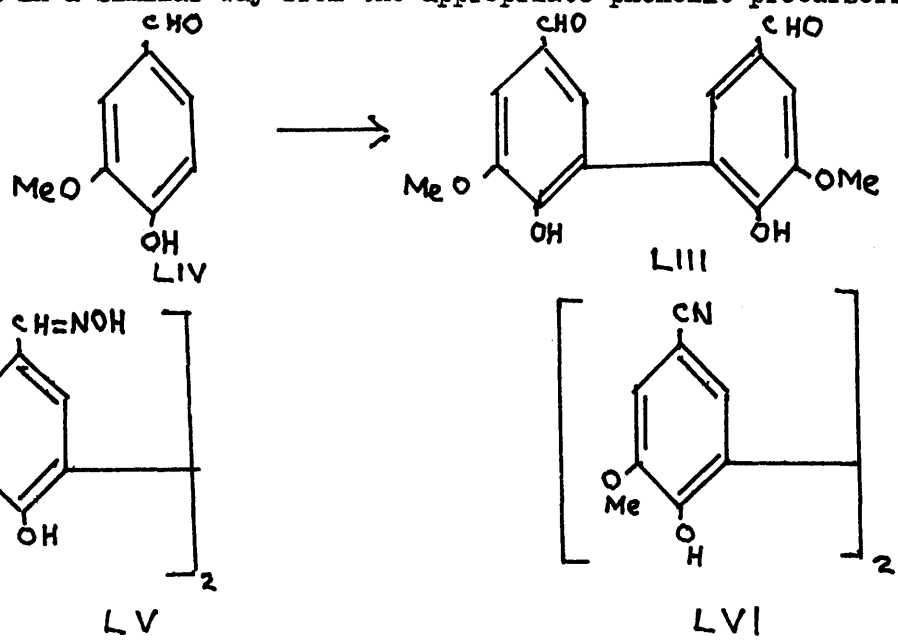


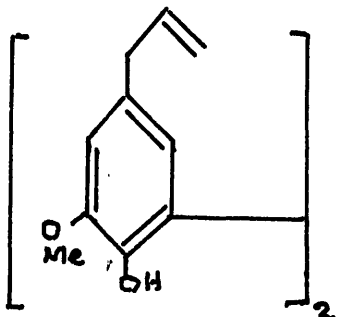
It may be noted that all the above products, except (LII), still contain one or two free hydroxyl groups with some of the ortho and para positions free and can obviously undergo further oxidative coupling in the same way as the parent phenol furnishing trimers and polymers. Actually also, some such trimers, as will be shown in the sequel, have been isolated and characterised in certain cases.

Before we take up some of the pertinent examples illustrating these modes of union, it may be pointed out in passing that the step involving tautomerisation of the initially coupled products like (XLVIIa) - (LIa) to appropriate phenolic equivalents, say (XLVIIb) -

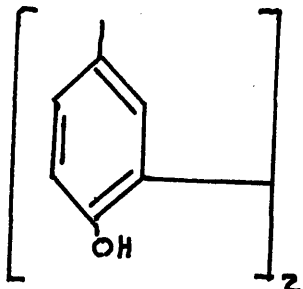
(LIb), will be assumed throughout in the sequel.

Some of the examples that come under the category of 'ortho-ortho carbon-carbon' coupling are provided by dehydrodivanillin (LIII) [47], [48], obtained by the oxidation of vanillin (LIV), dehydrodivanillin oxime (LV) [49], dehydrodivanillonitrile (LVI) [49], dehydrodieugenol (LVII) [7], dehydrodi-para-cresol (LVIII) [33], [34], [50], [51], [52], [53], dehydrodi-2:4-dimethylphenol (LIX) [33], [51], [54], dehydrodi-β-naphthol (LX) [55], dehydro-di-guaiacol (LXI) [56], dehydrodipyrogallol (LXII) [57], [58], dehydrodi-4-ethylpyrogallol (LXIII) [59], dehydro-di-p-ethylphenol (LXIV; R = Et) [54], dehydro-di-p-propyl phenol (LXIV; R = Pr) [54], dehydro-di-p-methoxyphenol (LXIV; R = OMe) [54], dehydro-di-4-methylguaiacol (OH = 1) (LXV) [54], and so on, all prepared in a similar way from the appropriate phenolic precursors.

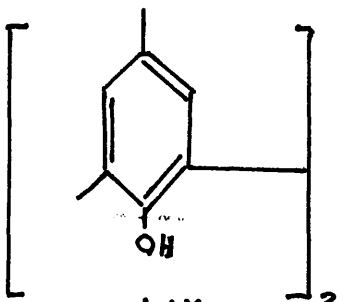




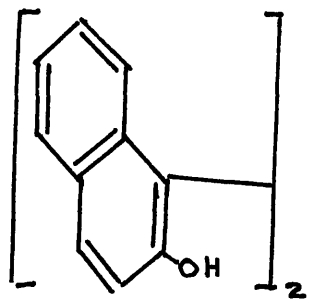
LVII



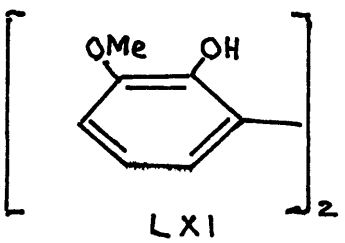
LVIII



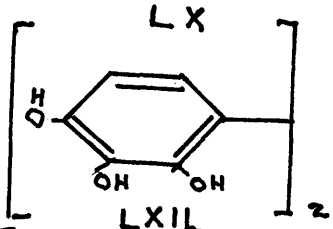
LIX



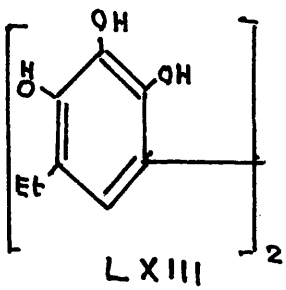
LX



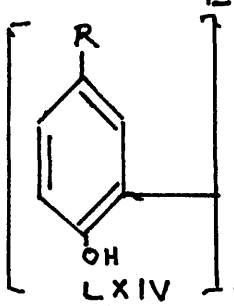
LXI



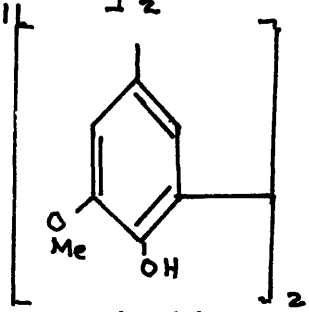
LXII



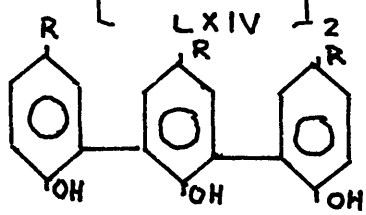
LXIII



LXIV



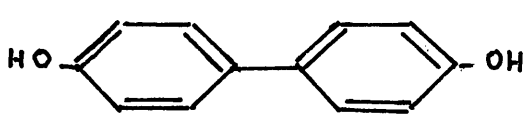
LXV



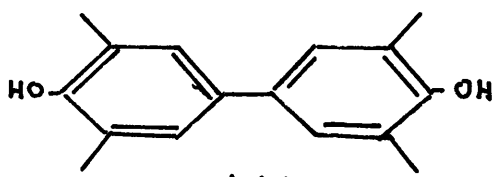
LXVI

It may also be noted that besides the dimers mentioned above, trimers (LXVI; R = Me or Et) have also been isolated from the oxidation of the corresponding phenols, viz. p-cresol and p-ethylphenol [50], [54].

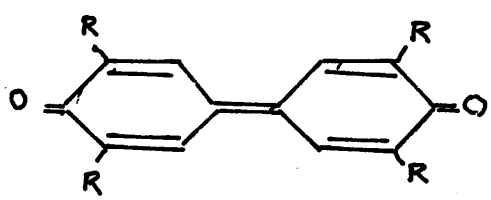
Examples of 'carbon-carbon para-para' coupling are furnished by 4:4'-dihydroxydiphenyl (LXVII) from the oxidation of phenol [34], [60], 3:5:3':5'-tetramethyl-4:4'-dihydroxydiphenyl (LXVIII) and 3:5:3':5'-tetramethyl-4:4'-diphenoquinone (LXIX; R = Me) from 2:6-dimethylphenol [32], [33], [34], [51], [54], 4:4'-dihydroxy-3:3'-dimethyldiphenyl (LXX) [34] and 3:3'-dimethyl-4:4'-diphenoquinone (LXXI) [2c] from o-cresol, (LXXII] from anthranol [25], [61], 2:3:6:7-tetraacetoxy-9:10-dihydro phenanthrene (LXXIII) from the oxidation of 3:4:3':4'-tetrahydroxybibenzyl (LXXIV) followed by reductive acetylation of intermediate quinone (LXXV) [62], 3:5:3':5'-tetramethoxy-4:4'-diphenoquinone (LXIX ; R = OMe) [63], [54] from 2:6-dimethoxyphenol, 3:5:3':5'-tetra-tert.-butyl-4:4'-dipheno quinone (LXIX ; R = t-Bu) [64] from 2:6-ditert-butylphenol, and so on.



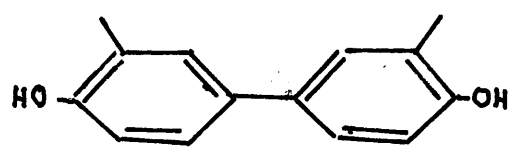
LXVII



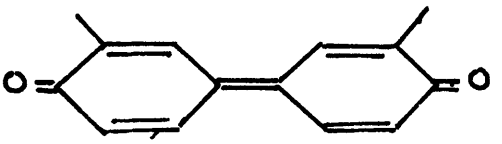
LXVIII



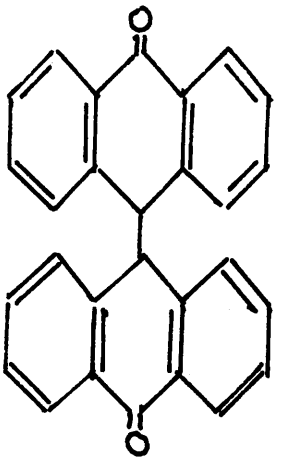
LXIX



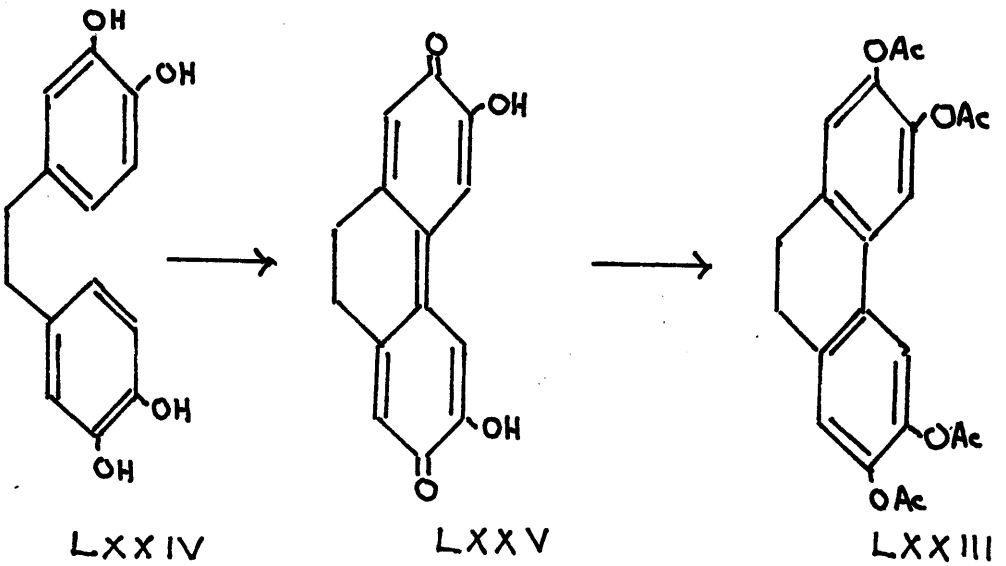
LXX



LXXI

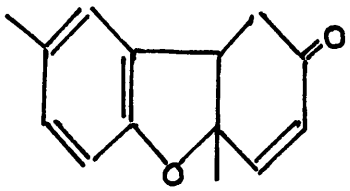


LXXII

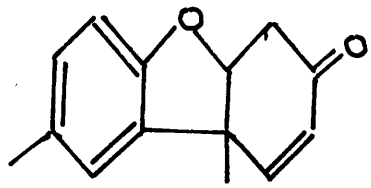


LXXIV LXXV LXXIII

Examples of 'carbon-carbon ortho-para' coupling are relatively less frequent. However, the dimeric neutral ketone [50], [51], [52], [54] obtained by the oxidation of p-cresol is the best example of this type. This ketone originally represented by the erroneous structure (LXXVI) [65] has now been shown by Barton, Deflorin and Edwards [66] to have the structure (LXXVII). The impact of the



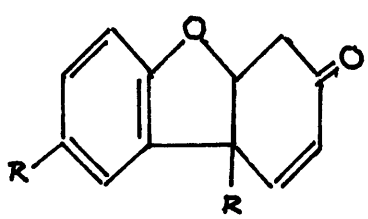
LXXVI



LXXVII

latter work on the mechanism of oxidation of phenols will be discussed shortly in a separate section.

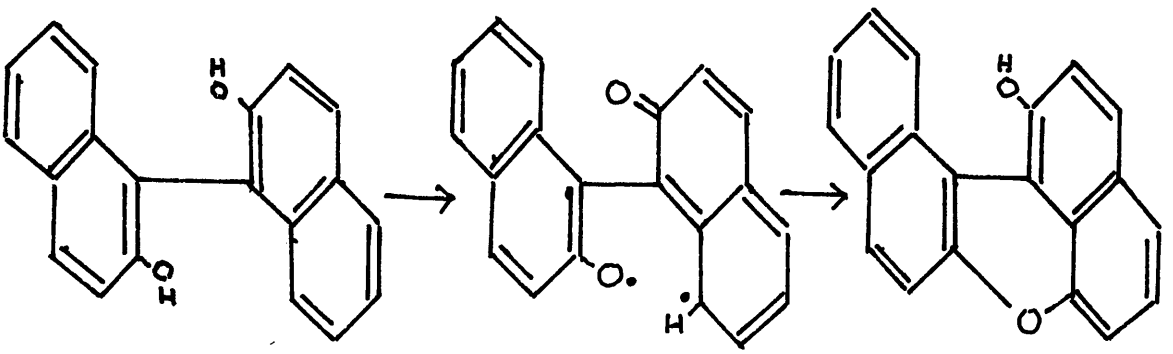
Analogous dimeric ketones (LXXVIII; R = Et or Pr) have recently been obtained by the alkaline ferricyanide oxidation of the corresponding para-alkylphenols [54]. Haynes et al. [54] have also reported the formation of ketonic dibenzofurans on the oxidation of 2:4-dimethyl and 3:4-dimethyl-phenols.



LXXVIII

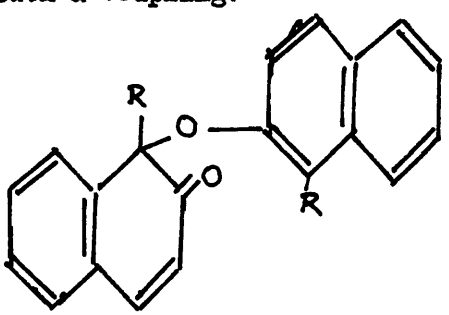
Carbon-oxygen coupling, although a less frequent occurrence, is nevertheless a well authenticated process. The oxidation product of dehydro-di-β-naphthol (LX) has been assigned the structure (LXXIX) [10], [12], [67], and most probably it involves a carbon-oxygen coupling

of the intermediate diradical (LXXX).

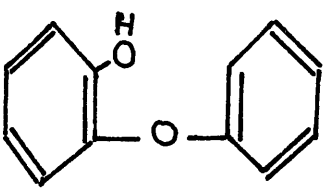


LX LXXX LXXIX

Oxidation products of 1-methyl-2-naphthol and 1-bromo-2-naphthol have been formulated as (LXXXI; R = Me) [25], [68] and (LXXXI; R = Br) [69] respectively. Obviously, these compounds incorporate such a coupling.

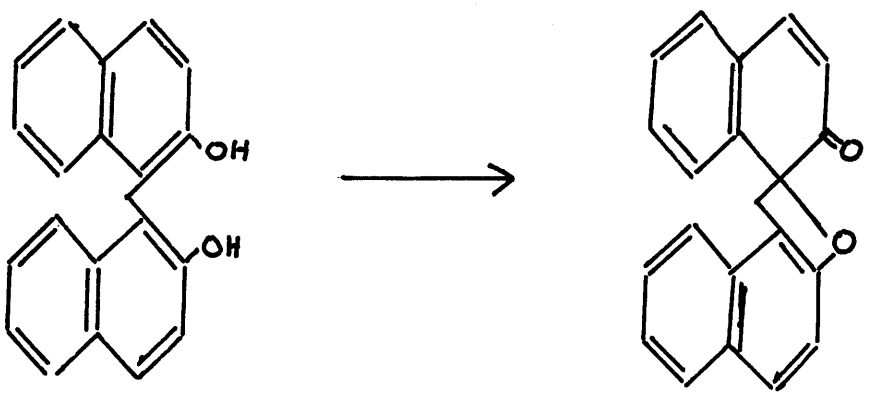


LXXXI



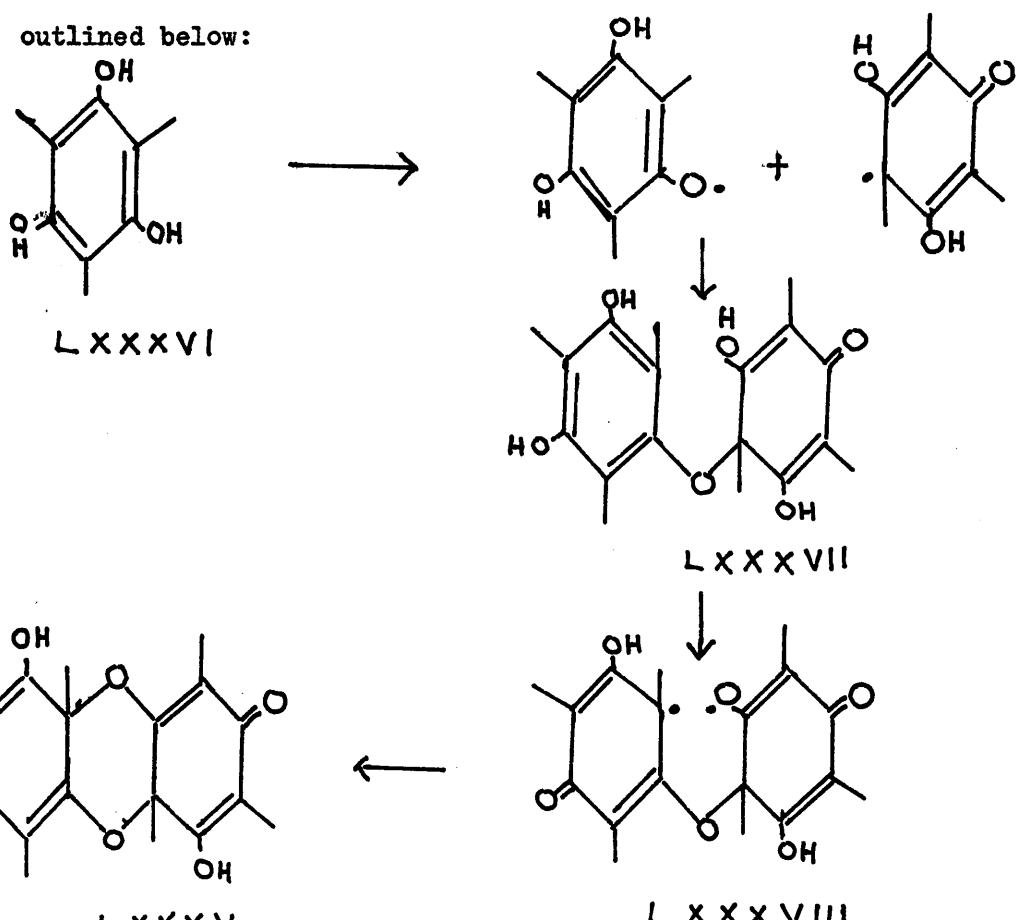
LXXXII

Anodic oxidation of phenol has also afforded (LXXXII) [60] providing still another instance of such a linkage. The oxidation product (LXXXIII) [25] of the phenol (LXXXIV) provides another example of a carbon-oxygen union of intramolecular type



LXXXIV LXXXIII

'Cedrone' (LXXXV) [70], an oxidation product of trimethyl phloroglucinol (LXXXVI), also incorporates some kind of carbon-oxygen coupling at some stage. One possible mode of its formation is outlined below:

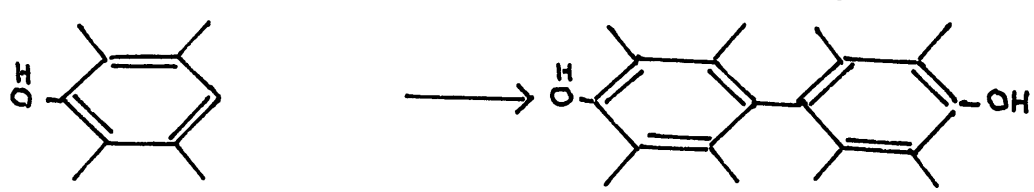


LXXXVI LXXXVII LXXXVIII LXXXV

It may be noted that the above scheme for the formation of 'cedrone' involves at one point an enolized 1:3-diketone (LXXXVII) which has been assumed to give a radical (LXXXVIII) just like phenols. Such an assumption is not entirely unreasonable as this radical, if formed, should also be resonance stabilised just like the phenoxy radicals.

Oxygen-oxygen coupling is even rarer. However, Goldschmidt and his co-workers [23], [71], [72] have already been said to have formulated the oxidation products of phenanthrols (XXXV; R = Me or Et or Cl or Br or Ph) as (XXXVI) implying, of course, an oxygen-oxygen union.

A few words at this stage about the enzymatic oxidation of phenols [56] should not be out of place. Quite a few cases of such oxidations 'in vitro' are reported in the literature affording similar products as are obtained by the oxidation of those phenols with inorganic reagents. Thus the enzymatic oxidations of p-cresol [73], vanillin [74], o-cresol [56],etc. have yielded similar products in the two cases. Durenol (LXXXIX) has been coupled enzymatically to dehydrodidurenol (XC). [56]



LXXXIX XC.

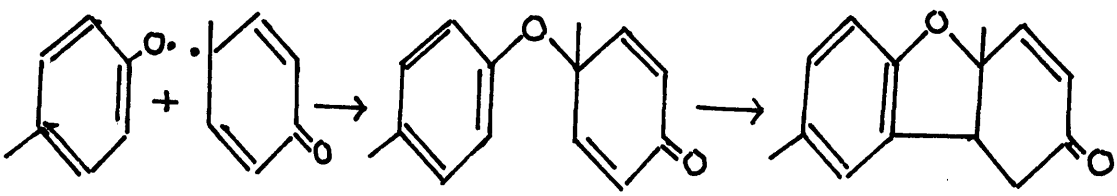
However, certain significant differences between the 'in vitro' and 'in vivo' enzymatic oxidations must be noted. The Pummerer's ketone (LXXVII), obtained by 'in vitro' enzymatic oxidation, for example, is still racemic.

Finally it would be pertinent to state briefly the position of the mechanism of oxidation of phenols as understood at the present time. We shall confine ourselves to oxidation by alkaline potassium ferricyanide, not because it is completely understood but because it is the oxidant that has been most extensively used for the oxidation of phenols, and is the oxidant of choice in the present work.

The ambiguity that has surrounded the mechanism of oxidation of phenols by ferricyanide is well illustrated by the erroneous formulation of several of the products obtained from various phenols. For example, the neutral ketonic dimer obtained by the oxidation of p-cresol had been assigned structure (LXXVI) [65] by Pummerer and his co-workers and this formulation had been generally accepted as late as 1953 [75]. Formation of the same dimer through alternative means of oxidation was taken as a conclusive evidence for this structure. However, Barton, Deflorin and Edwards [66] have recently established decisively the erroneous nature of this structure and have shown that it rested on ambiguous evidence. Two schemes had been advanced in

order to explain the mode of formation of the dimer (LXXVI). Pummerer et al. [65], [26], Schöpf [76] and others [77] believed the formation of the dimer (LXXVI) as proceeding through an intermediate (LXXVIa) as shown in Scheme I below:

Scheme I

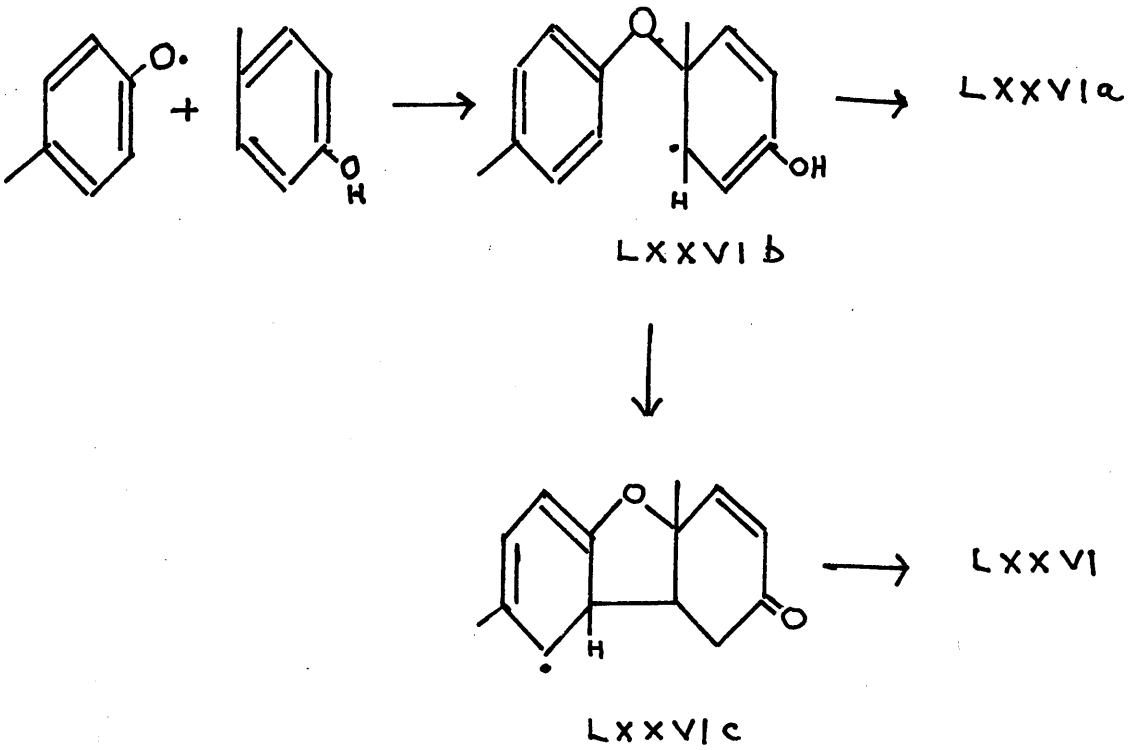


LXXVIa LXXVI

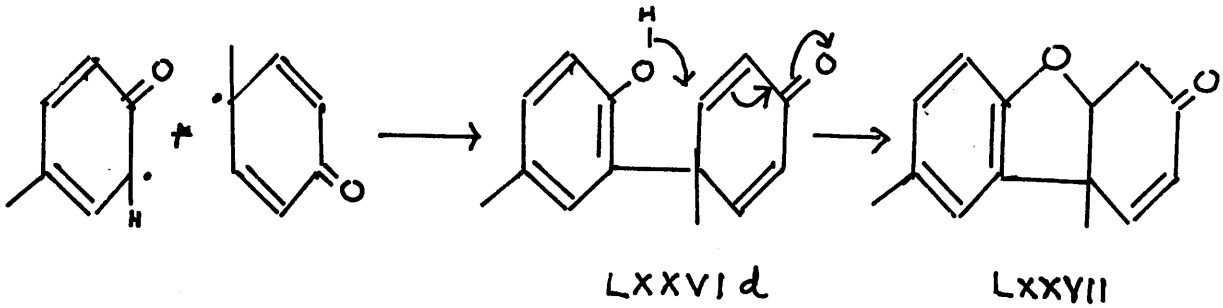
The change from (LXXVIa) to (LXXVI), however, appeared improbable.

The alternative scheme II considered an alternative mechanism of the formation of (LXXIV) which involved radical substitution using radicals (LXXVIb) and (LXXVIc) as intermediates. The radical (LXXVIb) is the same type of hemiquinone radical that is encountered in the oxidation of quinols and catechols and it would most probably be oxidised to (LXXVIa) rather than cyclise to (LXXVIc).

Scheme II

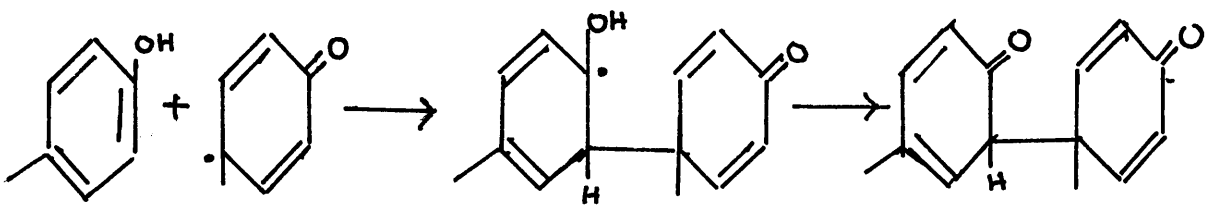


Barton et al. [66] clearly pointed out these theoretical difficulties in formulating this dimer as (LXXVI) which the earlier workers did not seem to appreciate. They further suggested the following alternative scheme for the dimerisation. It involved carbon-carbon coupling either by 'radical pairing' or 'radical substitution' [78] as the first step, followed by the β-addition of the phenolic hydroxyl to the enone system to give rise to the alternative structure (LXXVII) of this neutral, dimeric oxidation product of p-cresol. (LXXVId) was the first non-radical product suggested in this mechanism as outlined below:



LXXVI d LXXVII

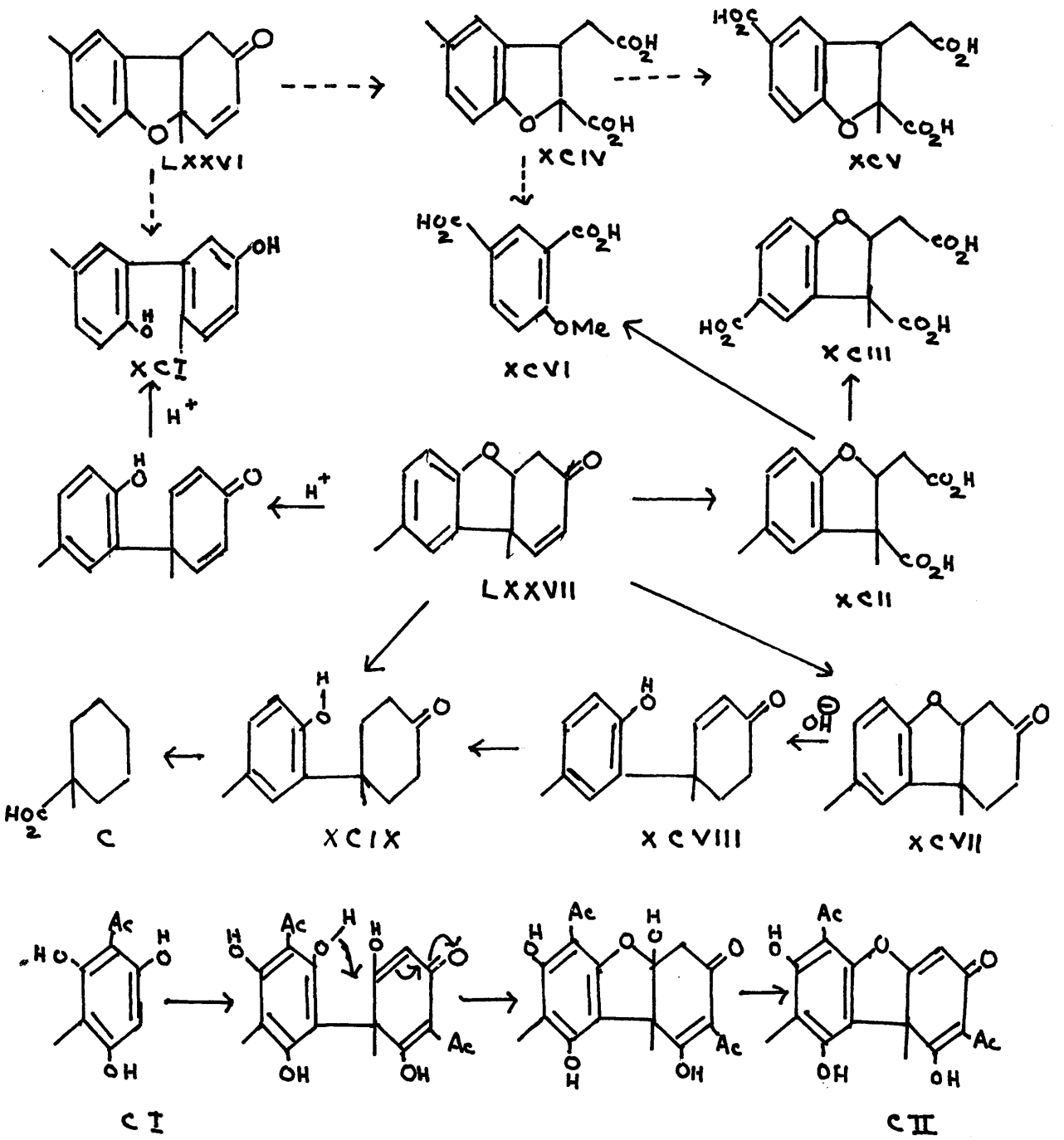
or alternatively,



LXX VI e LXX VI d

It is obvious that the latter scheme does not suffer from the theoretical difficulties referred to above in reference to the earlier two schemes. Moreover, the revised structure (LXXVII) for Pummerer's ketone accords not only with all the earlier ambiguous evidence adduced in support of the structure (LXXVI) but it is also in agreement with some further evidence given in its favour by Barton et al. Thus, the dienone-phenol rearrangement would easily explain the formation of 2:5'-dihydroxy-5:2'-dimethyldiphenyl (2:3'-dicresol)

(XCl), the dicarboxylic acid and tricarboxylic acid obtained by permanganate oxidation would have the revised structures (XCII) and (XCIII) instead of the earlier structures (XCIV) and (XCV) respectively. Further, hydrogenation of (LXXVII) gave a dihydro derivative (XCVII), showing a spectroscopic behaviour consistent with its structure, which resisted further hydrogenation in neutral medium but took up a second mole of hydrogen in ethanolic sodium ethoxide over palladised charcoal to give the ketophenol (XCIX) with expected bands in the infrared spectrum. The keto-phenol (XCIX) could also be obtained in one step by a similar hydrogenation of the dimer (LXXVII). Wolff-Kishner reduction of (XCIX) followed by permanganate oxidation afforded 1-methylcyclohexane-1-carboxylic acid (C). The theoretical soundness of this mechanism of the formation of Pummerer's ketone was finally crowned by an elegant two-step synthesis of the lichen substance usnic acid (CII) by the similar oxidation of C-methylphloroacetophenone (CI) according to a scheme based on a similar line of arguments. [See CI $\rightarrow$ CII].


LXXVI
XCIV
XCV
XCI
XCVI
XCIII
H+
LXXVII
XCII
C
XCIX
XCVIII
XCVII
CI
CII

While the formation of products of the kind discussed above can be explained in terms of 'radical pairing' or 'radical substitution' of the mesomeric aryloxy radicals, Haynes et al. [54] during their kinetic suudies of the ferricyanide oxidation of phenols have suggested the possibility of the coupling process being heterolytic, in view of the fact that the oxidation products invariably appear to have aromatic nuclei coupled together only in ortho- or para positions to the original hydroxyl groups. This heterolytic mechanism would involve a cationoid substitution of a phenolate anion by a mesomeric aryloxy cation formed by a second stage oxidation of the initially formed aryloxy radical by one electron abstraction.

$$ArO^- + [Fe(CN)_6]^{3-} \rightleftharpoons ArO\cdot + [Fe(CN)_6]^{4-}$$

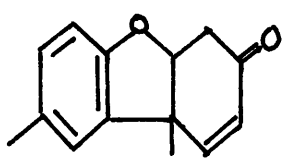
$$ArO\cdot + [Fe(CN)_6]^{3-} \longrightarrow (ArO)^+ + [Fe(CN)_6]^{4-}$$

$$ArO^+ + ArO^- \longrightarrow \text{Diaryls or aryl ethers}$$

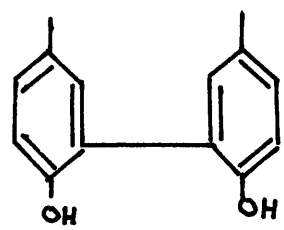
This mechanism is also in agreement with the fact that under varied conditions, the oxidation always requires the consumption of more than one equivalent of ferricyanide. However, it has been found that in all the oxidations, only part of the products could be separated into these ketonic and phenolic dimers while considerable amounts are chemically intractable resins probably arising out of consecutive

oxidations of the dimers. These and other factors complicate the interpretation of the kinetic data on the oxidation of phenols. Still, certain conclusions have emerged from the studies of Haynes et al. [54] and these can best be summed up as follows:-

(a) In the oxidation of p-cresol, for instance, the complexity of the reaction increases with the alkalinity of the medium, but the yield of Pummerer's ketone (LXXVII) is constant enough to indicate that the initial reaction may be giving (LXXVII) and (LVIII) in constant proportions and thereafter oxidation of the polyphenols may occur preferentially.



LXXVII



LVIII

(b) The velocity of oxidation increases with alkalinity in such a way as to indicate that the oxidisable organic substances are aryloxy-anions and not phenol molecules.

(c) Velocities of oxidation decrease, at all stages, with increase of ferrocyanide concentration, and this is what will be expected if the primary oxidation is the reversible one-electron transfer furnishing

mesomeric aryloxy radicals.

(d) The complexity of the oxidation is so great that no firm conclusions can be drawn concerning the order of the reaction with respect to the phenol. No simple kinetic expression can, therefore, be derived for these phenol oxidations.

(e) Though it is possible to prepare oxidant mixtures which do not detectably oxidise phenols though they may still contain high concentrations of the oxidant, it is not valid to extrapolate reaction-velocity-concentration graphs and thereby deduce "critical oxidation potentials" of quantitative significance [79].

In short, the only valid conclusions that appear to have been established in connection with the oxidation of phenols by alkaline ferricyanide are that the initial stage of oxidation of phenols by alkaline ferricyanide is a reversible reaction between the phenol anion and the ferricyanide ion, giving ferrocyanide ion and a mesomeric aryloxy-radical. Irreversible reactions then follow, giving mixtures of dimeric and polymeric products. It is the diversity of the aryloxy-radical itself that in the main obscures the elucidation of the reaction mechanism as it will be noticed that these complex features of phenol oxidation such as polymer formation are not peculiar to ferricyanide oxidations alone but are encountered elsewhere [see 51], e.g. in anodic oxidations.

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1. For leading references see, for example

   (a) Dianin, Ber., 1873, 6, 1252; 1874, 7, 125, 487; 1875, 7, 166.

   (b) Hofmann, Ber., 1878, 11, 329, 797.

   (c) Tiemann, Ber., 1885, 18, 3493.

   (d) Perkin et al., J., 1903, 192; 1904, 243.

   (e) Cousin and Herissey, Bull. Soc. chim. France, 1908, 3, 1066, 1070.

   (f) Fichter et al., Helv. Chim. Acta, 1925, 8, 332.

2. See, for example

   (a) Müller et al., Chem. Ber., 1957, 90, 2660; and earlier papers.

   (b) Cook et al., J. Org.Chem., 1958, 23, 755; and earlier papers.

   (c) Goldschmidt et al., Annalen, 1930, 478, 1; and earlier papers.

   (d) Pummerer et al., Chem. Ber., 1953, 86, 412; and earlier papers.

3. See, for example

   (a) Rosenwald, Hoatson, and Chenicek, Ind. Eng. Chem., 1950, 42, 162.

   (b) Bolland, Quart. Reviews, 1949, 3, 9.

   (c) Bolland and Ten Have, Trans. Faraday Soc., 1947, 43, 201.

4. (a) Barton and Cohen, "Festschrift Arthur Stoll", Birkhauser, Basle, 1957, p.117.

   (b) Erdtman and Wachtmeister, op. cit., p.144.

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THE ROLE OF PHENOL COUPLING IN THE BIOGENESIS OF NATURAL PRODUCTS.

The biogenetic significance of the reaction mechanism - oxidative coupling of phenol radicals - (see Chapter I) has been recognised long since [1], [2] and particularly appreciated in more recent times [3], [4]. It is now proposed to give a review of the various attempts, speculative as well as the ones realised experimentally, that have been made so far to correlate the structures of certain natural products in terms of this reaction mechanism.

Before we take up the review proper, it is appropriate at this stage to make some general observations in order to avoid repetition.

The fact that the modes of possible biogenesis in the sequel are set out as a connected series of reactions does not in any way imply a definite order followed by the plant also. This has been done just to achieve clarity of presentation and all such processes as O-methylation, O-O-methylenation, N-methylation, O-acylation, N-acylation etc., should be regarded as extra skeletal and can occur at any convenient stage of an assumed synthesis.

In many formulae given, the phenolic hydroxyls have been protected by the use of R, R', etc.. These blocking groups, in Nature, symbolise a residue, possibly part of an enzyme surface, which

can be added to, or taken away from a phenolic hydroxyl in order to provide protection adequate to ensure a specific phenolic coupling of radicals. Nature does not necessarily employ crude blocking methods like alkylation, acylation etc. made use of in laboratory schemes.

The oxidative coupling of phenols in the following pages has been assumed to occur by radical pairing. The same molecular species can, however, be also obtained by one act of "radical substitution" into an aromatic nucleus followed by a further act of one electron transfer.

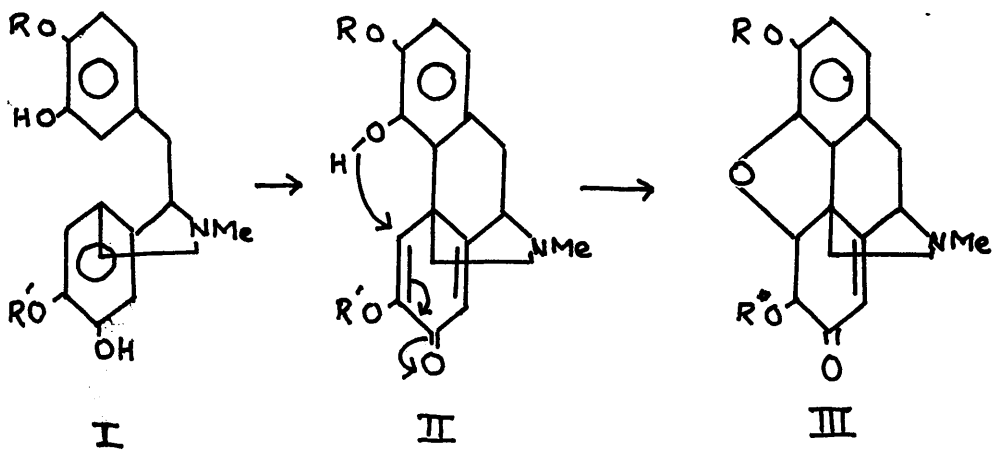
An abbreviation has been adopted in the various reaction schemes in that the tautomerisation of the coupled product to the appropriate aromatic equivalent has been assumed throughout.

Finally, the fact that a biogenetically plausible process of phenol coupling can be written does not mean that other equally plausible mechanisms cannot be devised. For example, while the biogenesis of morphine alkaloids has been postulated in the sequel in terms of radical pairing, another perfectly reasonable mechanism has been recently proposed by Cohen [5]. Final decisions on biogenesis can only be made by the appropriate but very laborious tracer experiments.

ALKALOIDS

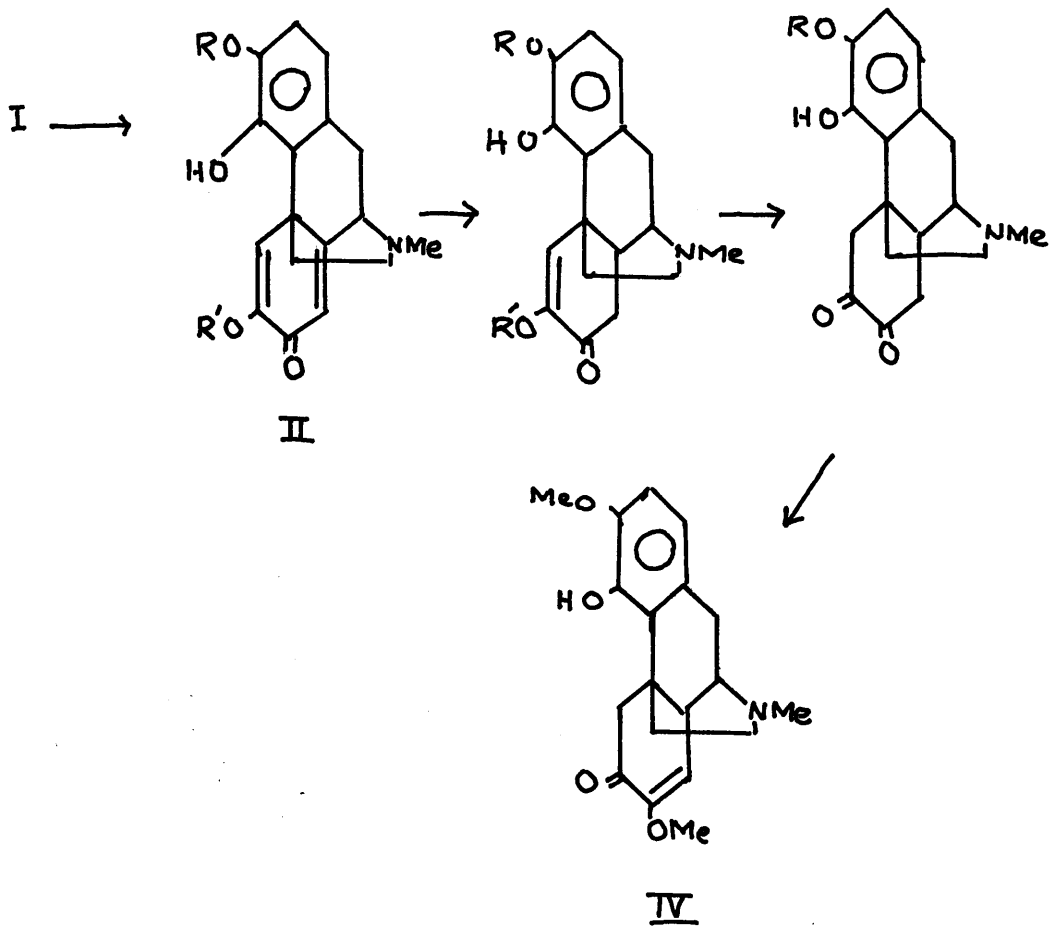
A. Morphine and Aporphine Alkaloids.

Barton and Cohen [3] have recently put forward a scheme for the biogenesis of morphine alkaloids. The essential details of this scheme are outlined below:-



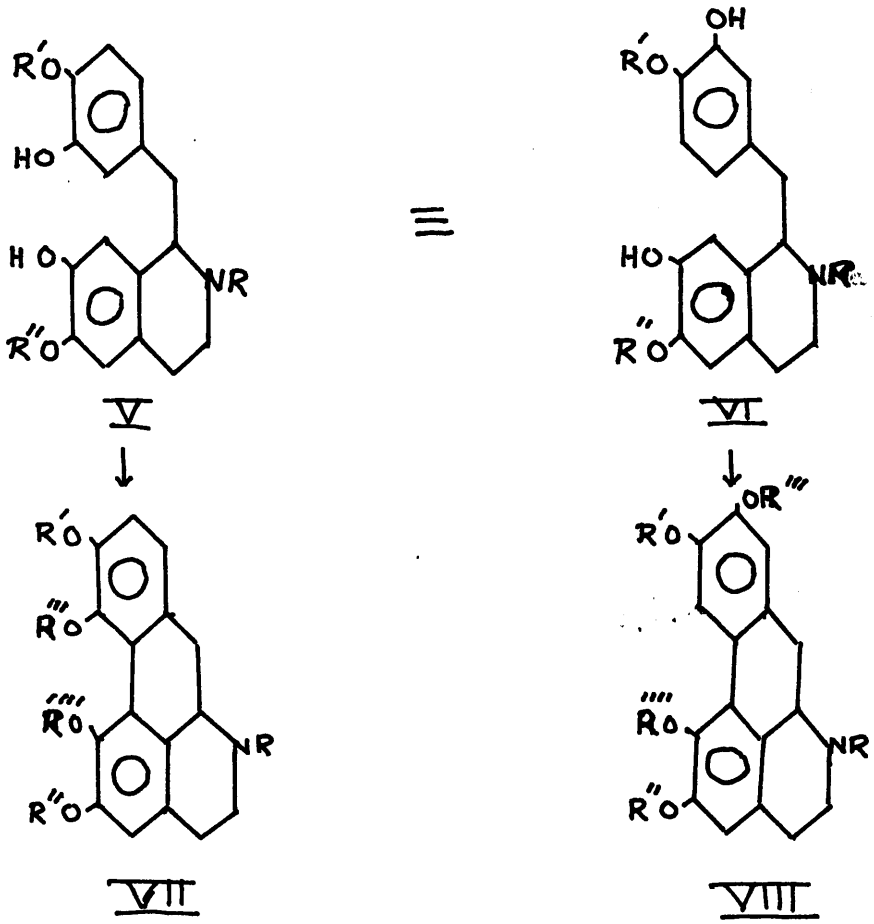
All the important morphine alkaloids like thebaine, oripavine, neopine, morphine and codeine can then be derived from (III) derived from the phenolic precursor (I) of benzylisoquinoline type.

Further, sinomenine (IV) can also be derived from (I) as indicated below:



IV

The majority of aporphine alkaloids [6] can also be built up by phenol coupling from V (≡ VI). The former gives rise to aporphine alkaloids (VII) of the corytuberine type, the latter alkaloids (VIII) of the glaucine type. [3], [4], [7].

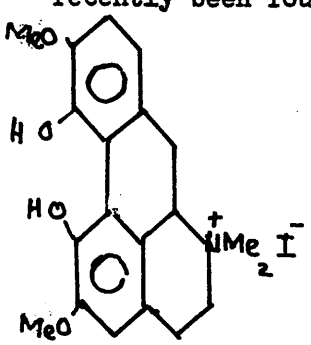


V ≡ VI

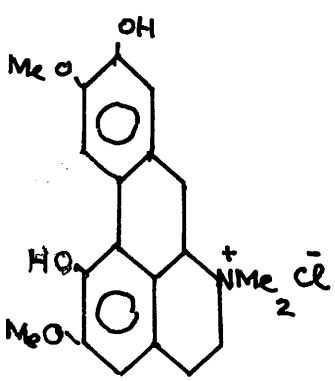
V → VII

VI → VIII

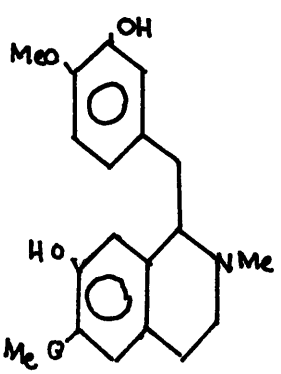
It is significant to note that laurifoline (IXa), magnoflorine (IXb) and coclanoline (X) besides coclaurine (XX; R' = H, R'' = Me) have recently been found in the same plant cocculus laurifoluis DC [8].



IX b



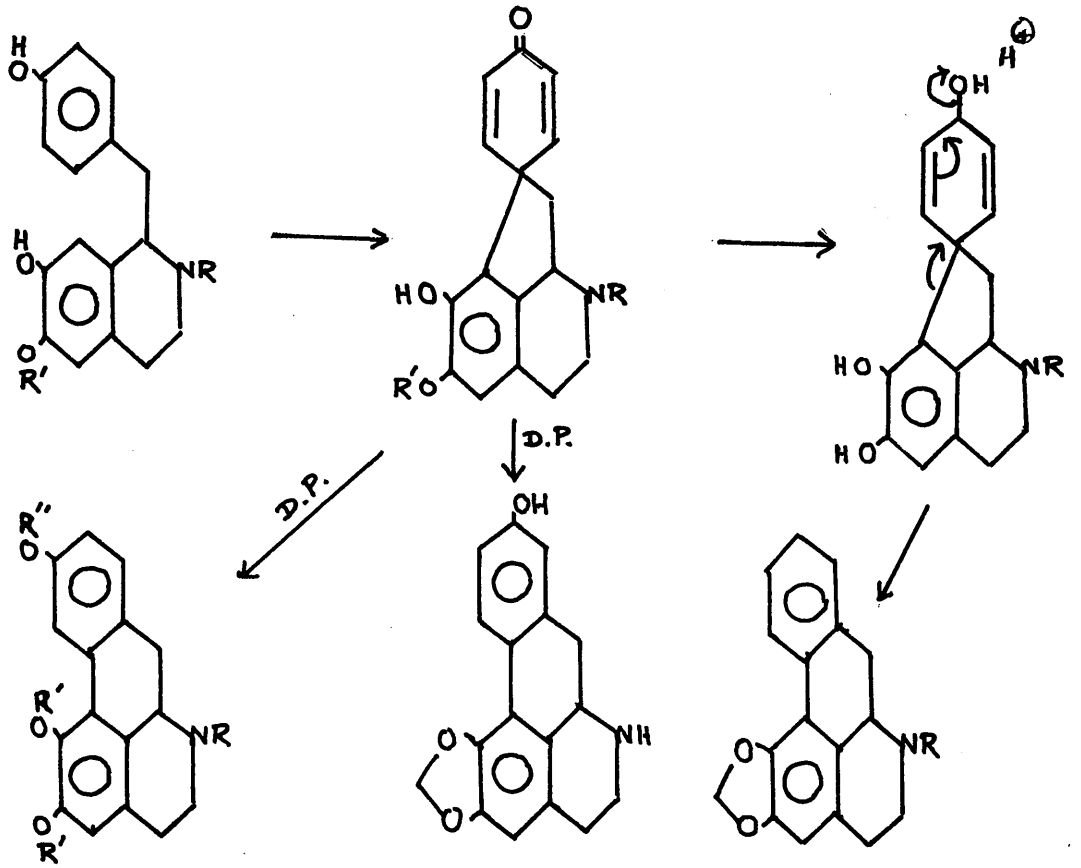
IX a



X

It is interesting to note that (X) has phenolic hydroxyl groups in the desired positions with free ortho- and para-positions necessary for oxidative coupling, to give the aporphines (IXa) and (IXb). Incidentally, it had been our object to synthesise a phenolic precursor of type (X) even before we were aware of the isolation and synthesis of these two compounds and see if we could develop conditions suitable for its conversion into aporphine bases of corytuberine and/or glaucine type and/or the precursor (III) for morphine alkaloids. (See Chapter IV, p.133).

There are several aporphines which present some difficulties in the rationalisation of their biogenesis through phenolic coupling. Barton and Cohen [3] have, however, suggested biogenetic pathways for these bases also in terms of the oxidative coupling of phenols. Thus, tuduranine (XI), laureline (XII), analobine (XIII), anonaine (XIV), roemerine (XV), crebanine [9] (XVI), stephanine (XVII) [115], isothebaine (XVIII) [10], [11] and pukateine (XIX) can also be built up through oxidative coupling of phenols as outlined below:



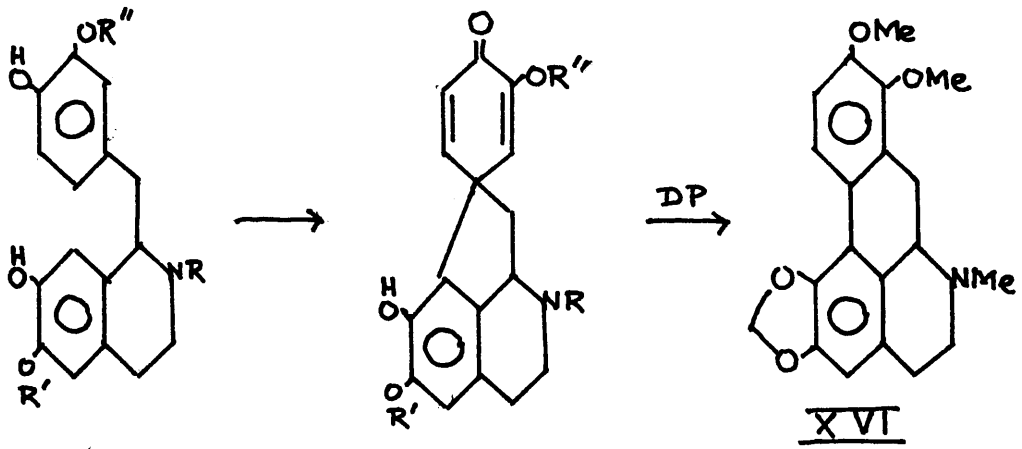
XI: R = R'' = H; R' = Me

XII: R = R'' = Me; R' = $-CH_2-$

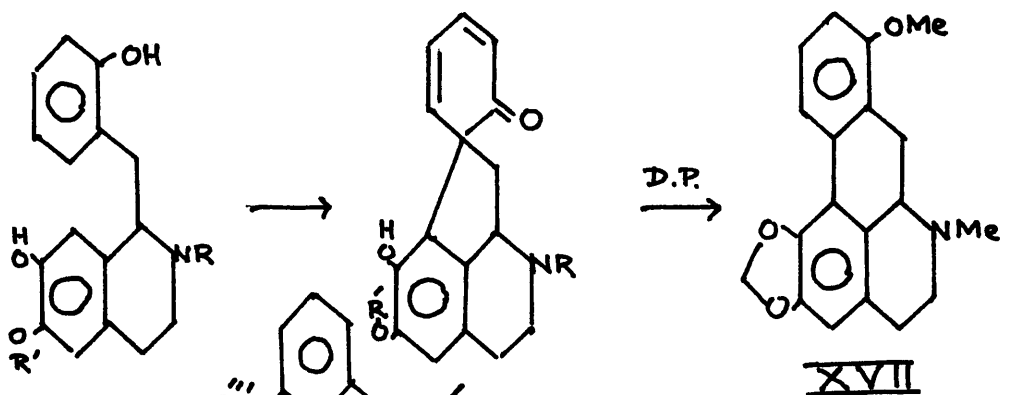
XIII

XIV: R = H

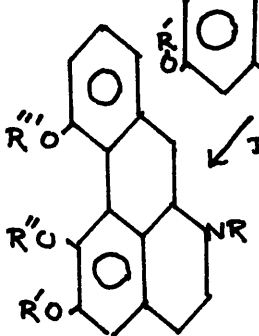
XV: R = Me



XVI



XVII



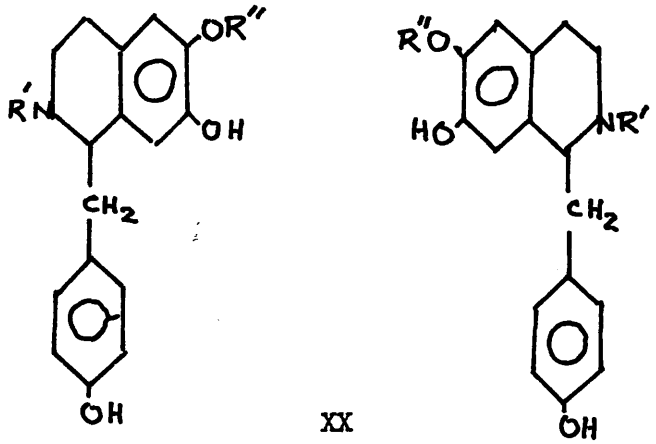
XVIII: R = R' = R''' = Me; R'' = H

XIX: R = Me; R' = R'' = $-CH_2-$; R''' = H

(D.P. represents the dienone phenol rearrangement which can occur in either of the two ways indicated).

B. Bisbenzylisoquinoline Alkaloids.

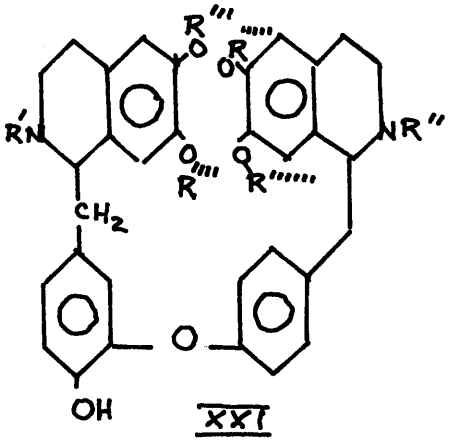
It has already been recognised [12], [13], [14] that the bisbenzylisoquinoline alkaloids [15], [16] are derived from coclaurine (XX; R' = H, R'' = Me) and its simple derivatives.



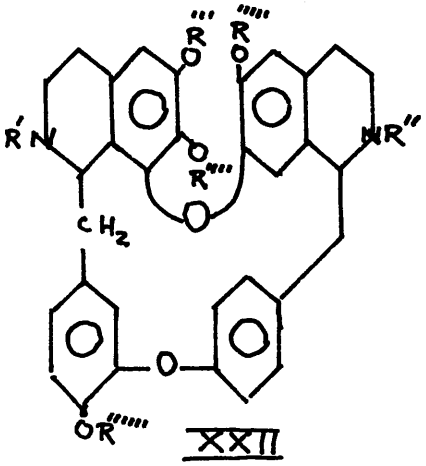
XX

The structural skeletons of all the bisbenzylisoquinoline alkaloids known hitherto can be represented by the formulae (XXI) to (XXIX). The formation of (XXI),(XXII), (XXIII), (XXIV) and (XXV) as a result of intermolecular carbon-oxygen coupling in suitable positions of two coclaurine molecules is fairly obvious and needs no further comment. Magnolamine (XXVI) and aztequine (XXVII), although belonging to the general type (XXI), contain one phenolic hydroxyl more than the bimolecular dehydrogenation product of norcoclaurine (XX; R' = R'' = H). They can be accommodated within this mode of biogenesis by the reasonable assumption that an extra hydroxyl group is introduced into the molecule either before or after the ether formation between two molecules of coclaurine or norcoclaurine. The structures (XXVIII) and (XXIX) represented by micranthine, menisarine, normenisarine; trilobine and isotrilobine present some difficulty, at first sight,

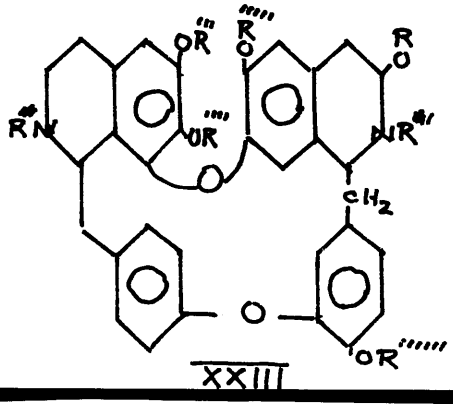
as regards their biogenesis by oxidative phenol coupling. However, Barton and Cohen [3] have overcome this difficulty by assuming a subsequent migration induced by the departure of a strongly electron-attracting residue, X (e.g. per-acid), as shown in the pathways (XXX) → (XXXI) and (XXXII) → (XXXIII).



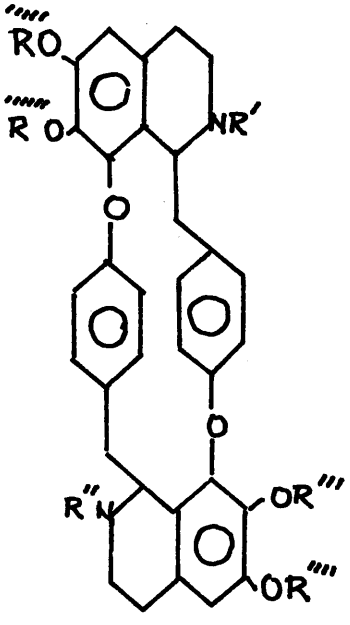
XXI



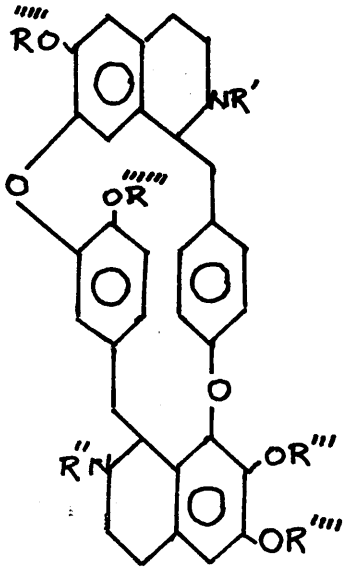
XXII



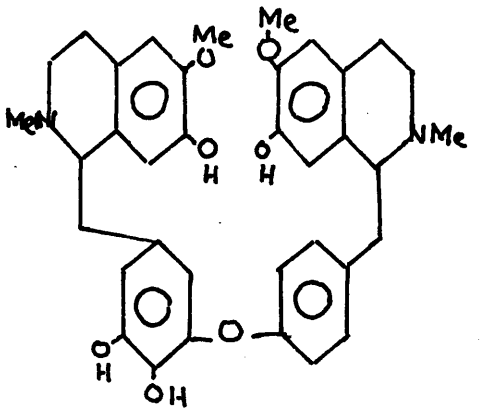
XXIII



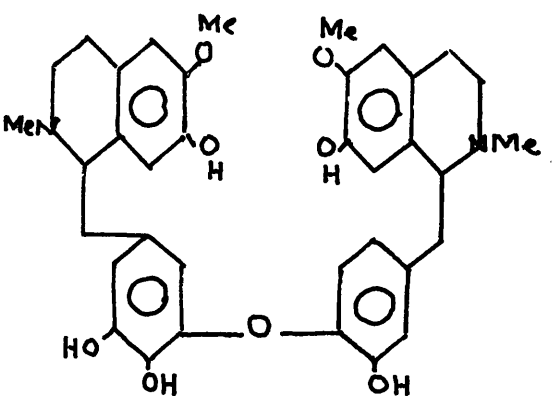
XXIV



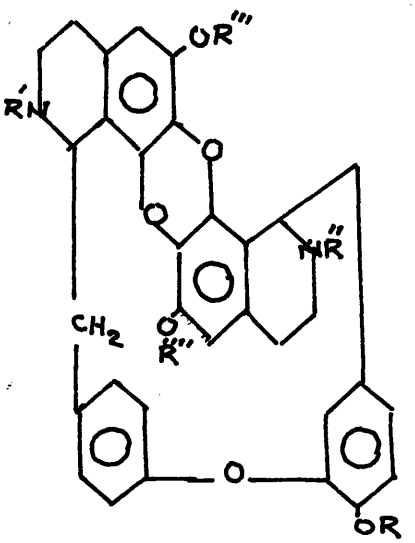
XXV



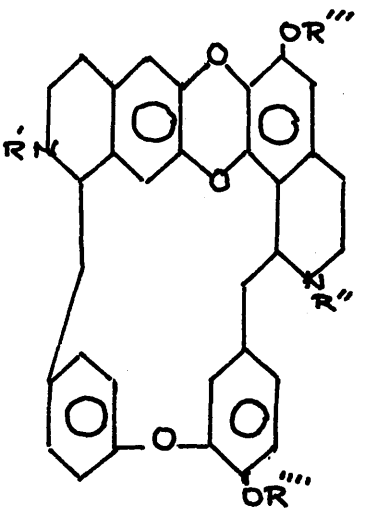
XXVI



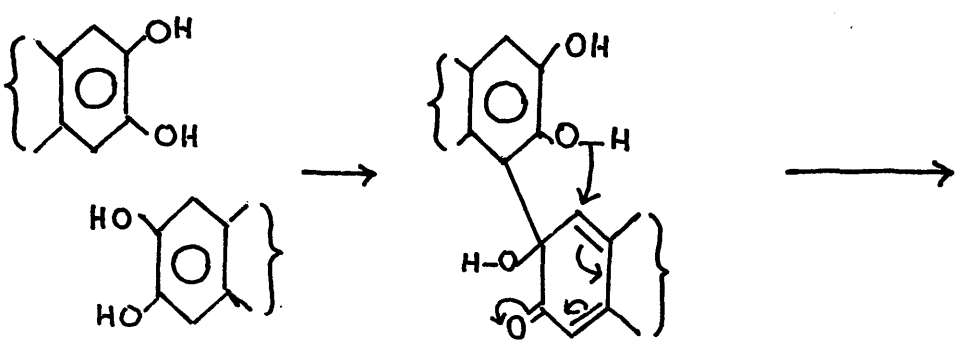
XXVII



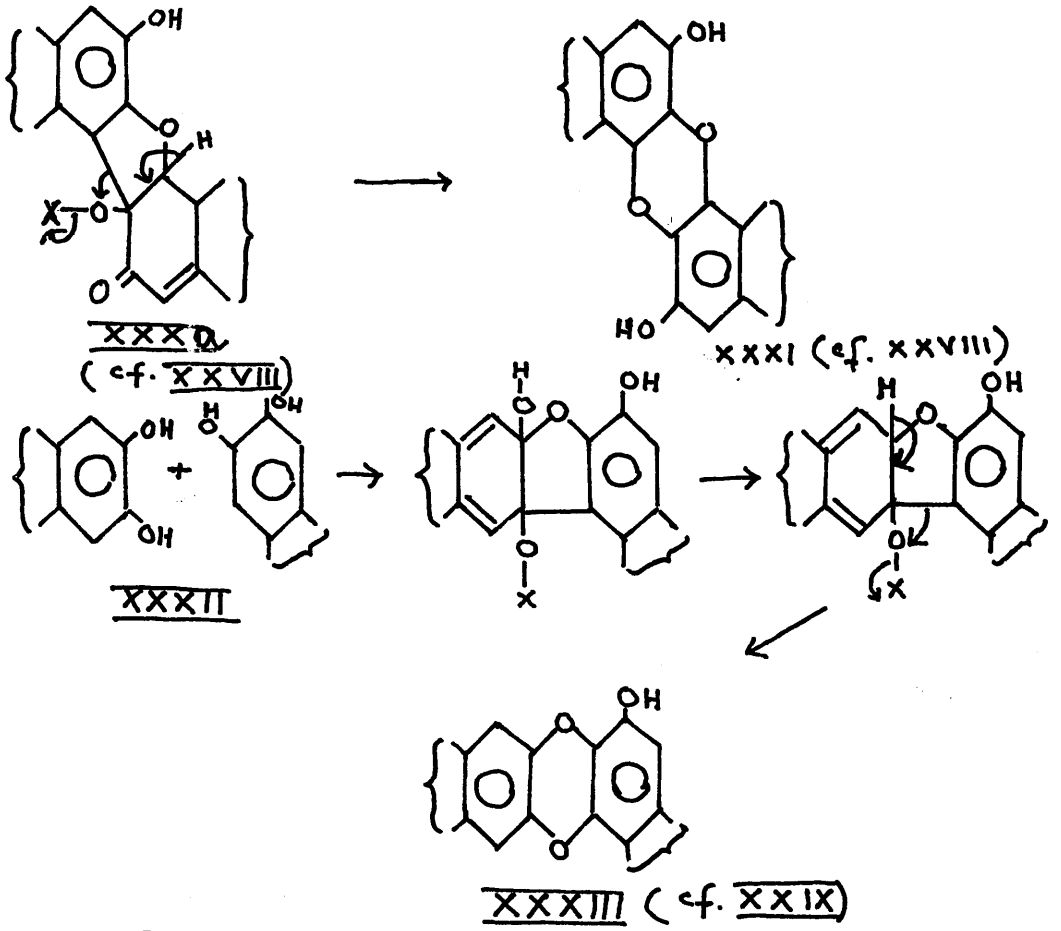
XXVIII



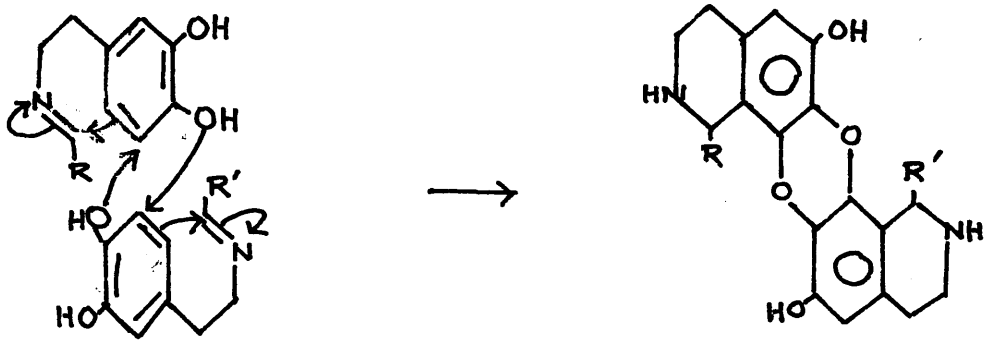
XXIX



XXX



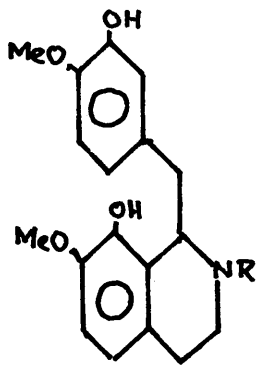
Cohen [5] has, however, proposed another mechanism for the genesis of menisarine type alkaloids which does not involve phenol coupling. (see XXXIV).



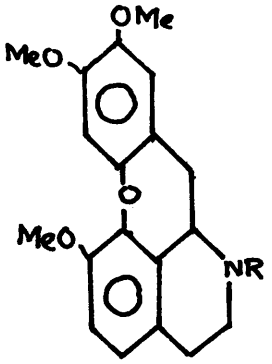
XXXIV XXXV

C. Cularine Alkaloids.

The alkaloids cularine (XXXVI; R = Me) and cularimine (XXXVI; R = H) [17] occur together in the same plant. The intramolecular 'carbon-oxygen' coupling of the benzylisoquinoline (XXXVII) should provide a simple biogenetic route for these compounds. [3], [4].



XXXVII

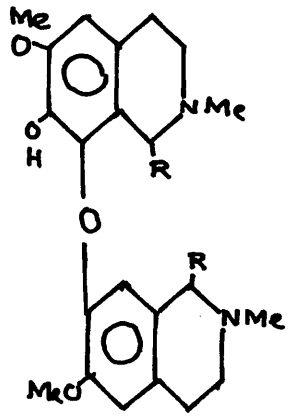


XXXVI

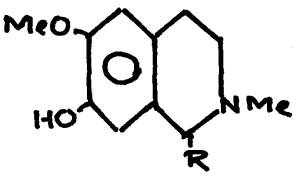
D. Cactus Alkaloids.

Although the cactus alkaloids known hitherto [18] consisted of molecules too simple to involve oxidative phenol coupling in their biogenesis, Djerassi and co-workers [19] have recently isolated three alkaloids, pilocereine, piloceredine and lophocerine from the cactus Lophocerus Schotti which clearly illustrates this mode of genesis. Pilocereine and piloceredine are diastereoisomers of the structure (XXXVIII) and lophocerine has the structure (XXXIX) and it is very

likely, as pointed out by Djerassi, that pilocereine and piloceredine are produced in the plant by the phenol coupling of two molecules of lophocerine.



XXXVIII

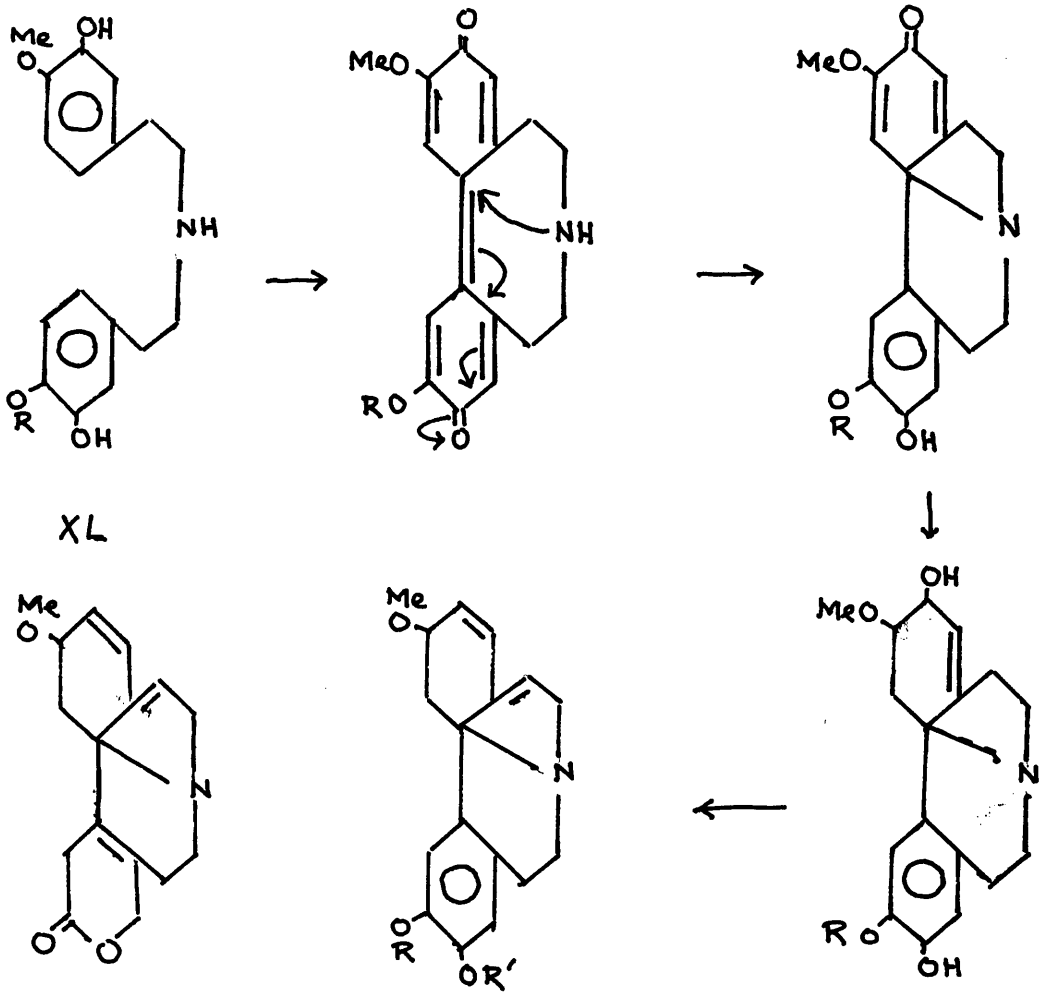


R = $-CH_2-CH<^{CH_3}_{CH_3}$

XXXIX

D. Erythrina Alkaloids.

The 'aromatic' erythrina alkaloids [20] erysopine (XLI), erysodine (XLII), erysovine (XLIII) and erythraline (XLIV) can arise from DOPA [25] via the base (XL) in accordance with the concept of oxidative phenol coupling as indicated [3]:-



XL

XLV

XLI: R = R' = H

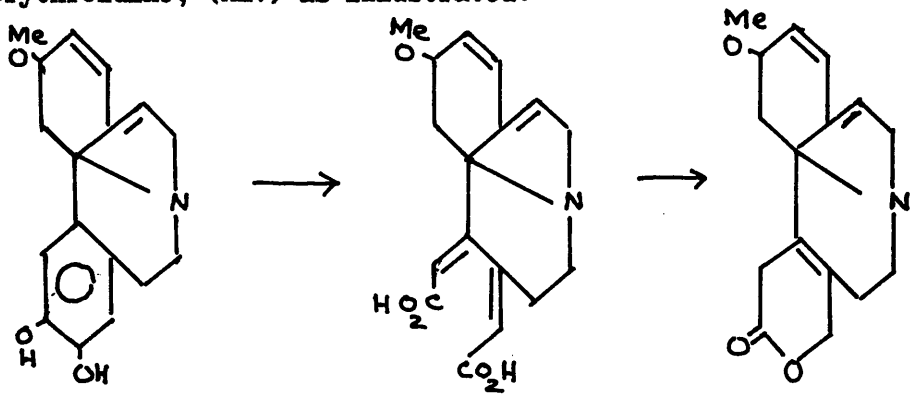
XLII: R = H; R' = Me

XLIII: R = Me; R' = H

XLIV: R = R' = $-CH_2-$

Some experiments along these lines carried out in this laboratory by Dr. J. Stouffer are briefly discussed on page 164 .

β-Erythroidine (XLV), a typical 'non-aromatic' erythrina alkaloid can be easily formed from erysopine (XLI) if it were imagined to undergo the Woodward fission [21], [22] of the catechol nucleus by some process similar to that proposed as one of the stages in the biogenesis of strychnine [22] and emetine [23]. Erysopine (XLI), on Woodward fission, would be expected to yield (XLIa) as an intermediate which, on decarboxylation and lactonisation, could readily give β-erythroidine, (XLV) as illustrated:-

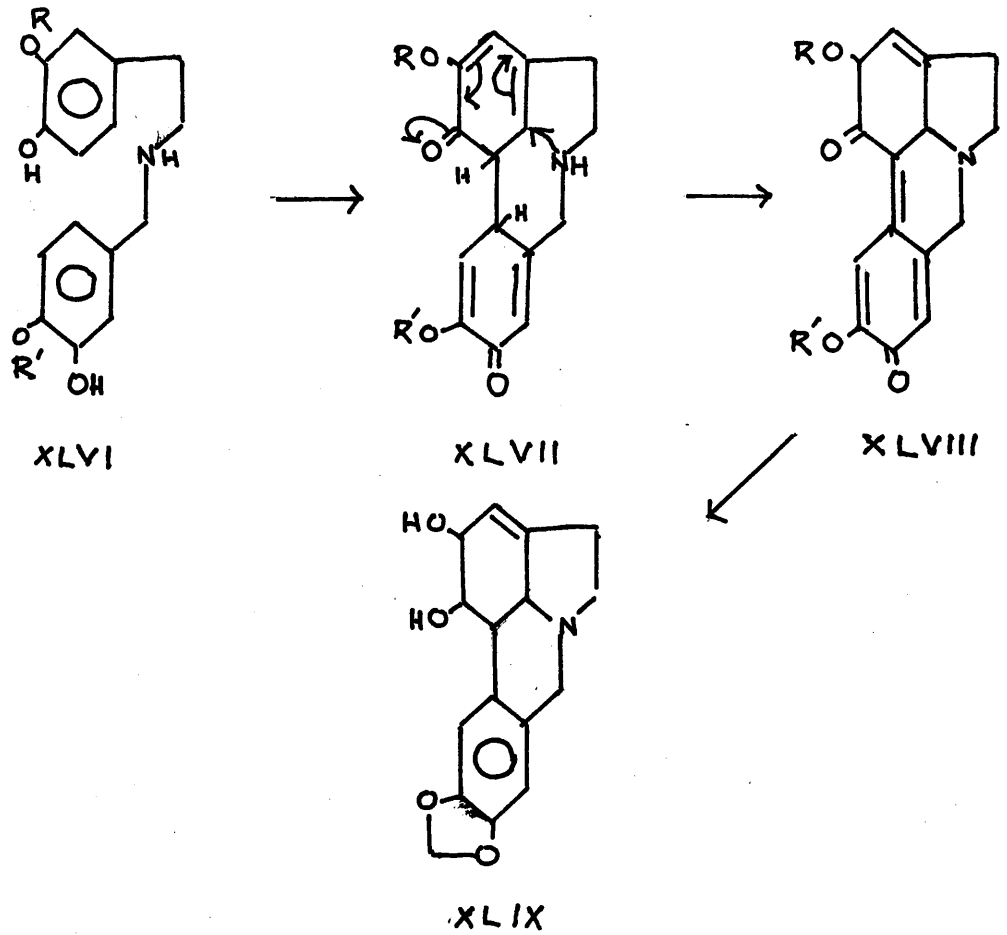


XLI XLIa XLV

It is significant to note that erysopine apparently occurs in all species of erythrina except those producing erythroidine [24].

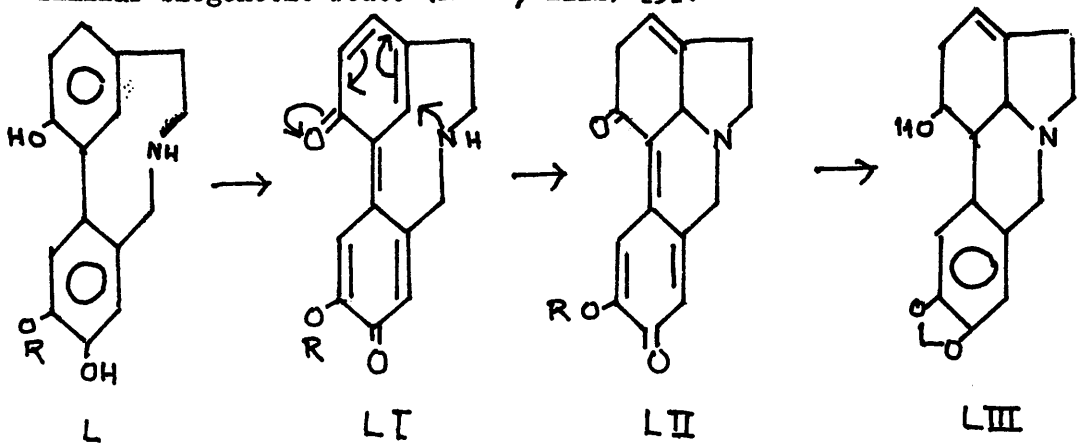
E. Amaryllidaceae Alkaloids.

The genesis of many of the Amaryllidaceae alkaloids can be based on a common type precursor using oxidative phenol coupling. Thus lycorine (XLIX) [26], [27], the major Amaryllidaceae alkaloid, can arise from (XLVI) through the following pathway (XLVI → LXIX) [26],[3].



XLVI XLVII XLVIII XLIX

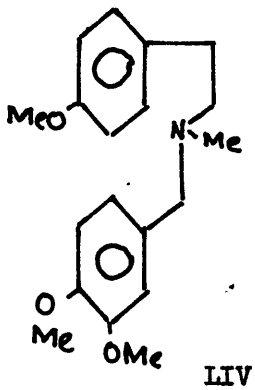
The alkaloid caranine (LIII) [28] also probably follows a similar biogenetic route (L ⟶ LIII) [3].



L LI LII LIII

Laboratory imitations of stages (XLVII ⟶ XLVIII) and (LI ⟶ LII) are available already [29], [7].

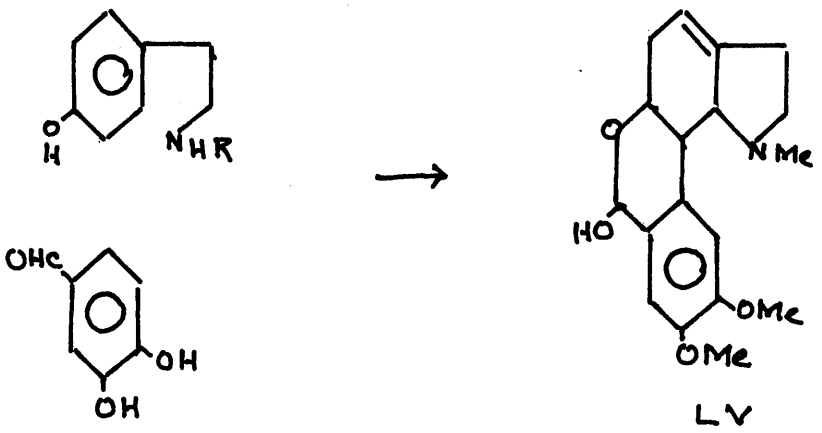
It is interesting to note that belladine (LIV) [30] has recently been isolated from the bulbs of an Amaryllis belladonna hybrid. It will be noticed that belladine (LIV) is just an O- and N-alkylated (methylated) product of (L), the precursor postulated by Barton and Cohen [3] for the amaryllidaceae alkaloid caranine (LIII). This precursor, being a stable compound, can conceivably undergo biological N:O-alkylation before oxidative coupling took place and thereby be prevented from oxidation to the theoretically possible caranine (LIII), the major alkaloid from this bulb.



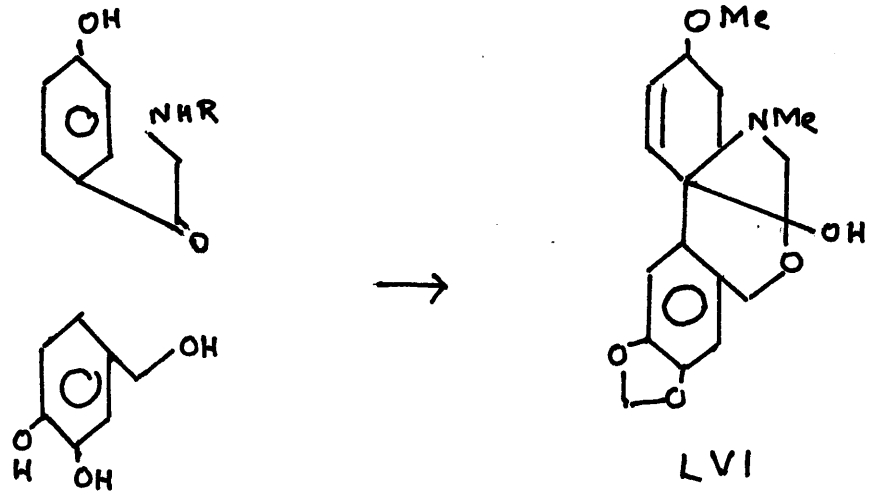
LIV

However, there are two minor amaryllidaceae alkaloids lycorenine (LV) [31] and tazettine (LVI [32] whose biogenesis presents some difficulties. These structures can possibly be accommodated

within the general concept of oxidative phenol coupling if one assumes the union of two separate radical fragments, rather than the intramolecular cyclisation of a single diradical [3].



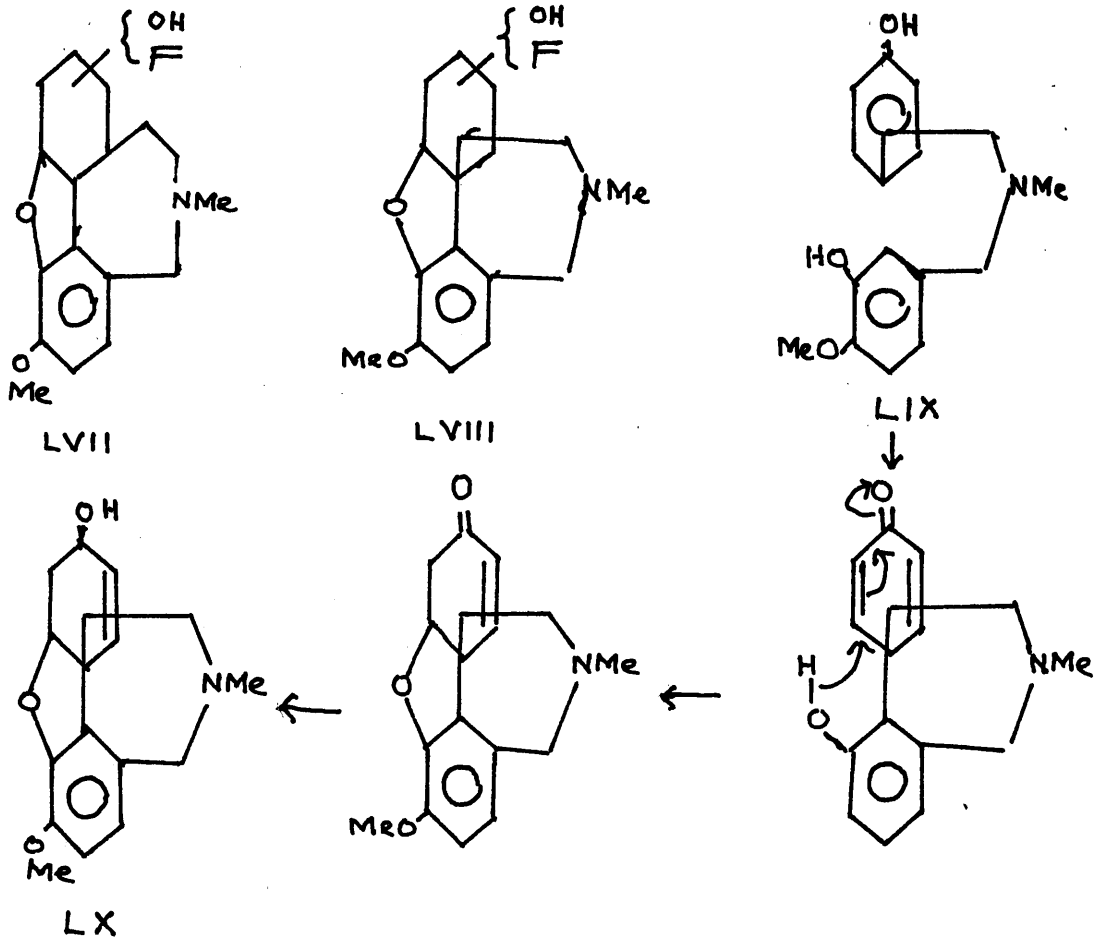
LV



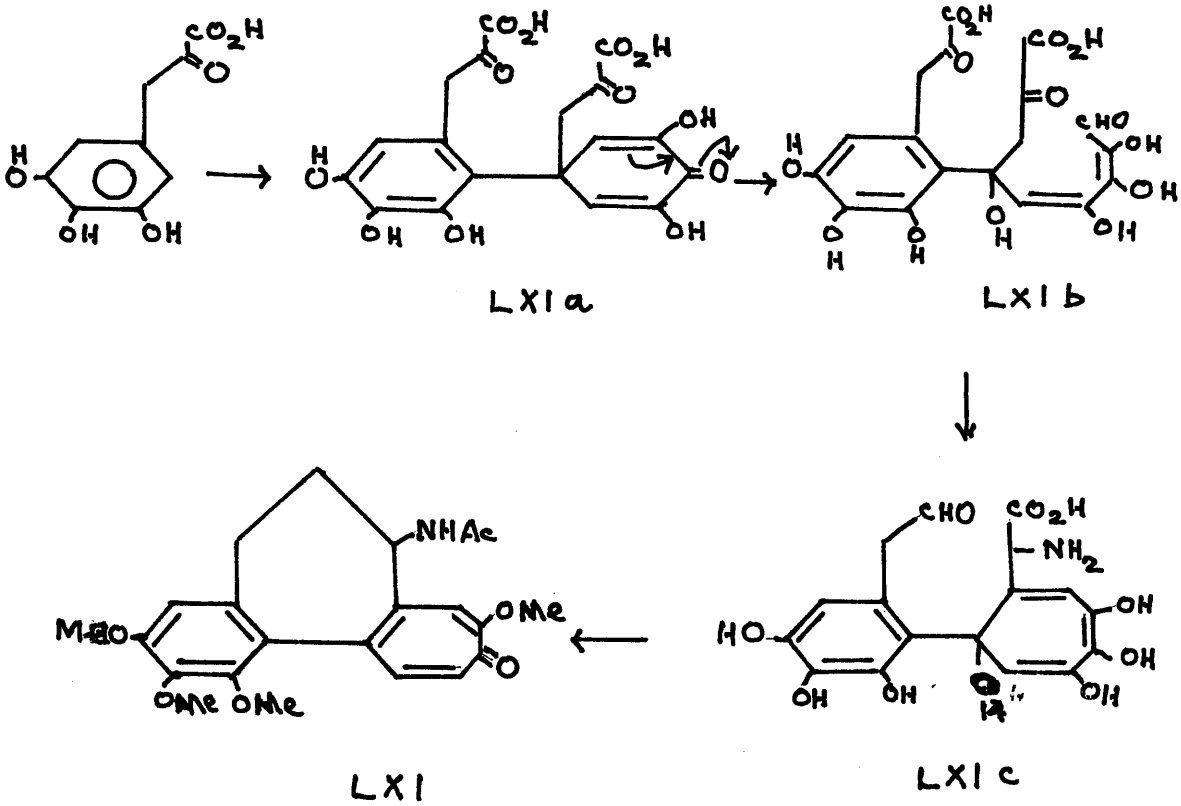
LVI

Galanthamine [33] has recently been represented by the two possible expressions (LVII) and (LVIII). It has been suggested [3] that the foregoing biogenetic considerations can be helpful in deciding the

correct structure. For example, a biogenetic precursor like (LIX) should lead to structure (LX) for galanthamine.



Colchicine (LXI) has also been accommodated within this general mode of biogenesis by Belleau [34] according to the following scheme involving at one stage the oxidative ortho-para coupling of two molecules of trihydroxyphenylpyruvic acid:



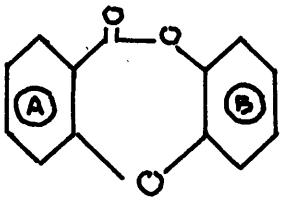
Formation of (LXIa) from trihydroxyphenylpyruvic acid is not without analogy. Such an oxidation and coupling of a pyrogallol type of compounds finds a basis in the elegant work of Critchlow, Haworth and Pauson [35] on the structure and mechanism of formation of purpurogallin. This is followed by an oxidative cleavage of (LXIa) to yield the seco-compound (LXIb) and the site of cleavage of (LXIa) is

determined by the resonance induced electron deficiency there [see arrows in (LXIa)]. The subsequent steps (LXIb) - (LXIc) are self explanatory.

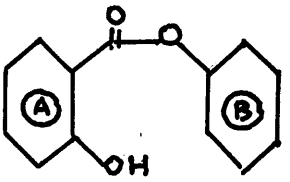
FUNGAL METABOLITES

The lichens were shown by Schwendener to be "symbiotic" with fungal and algal components as early as 1860 and since then our knowledge of the close relationship between the lichenous and fungal metabolism has increased. Compounds related to the phenolic lichen acids have been found among the products of fungal metabolism [36] and the fungal part of the lichens has been presumed to be responsible for the elaboration of these substances [37]. It would not, therefore, be out of place to consider the biogenesis of lichenous substances along with that of fungal metabolites.

Two of the main classes of lichen substances [37] are depsidones and depsides. The depsidones can be represented by the general skeleton (LXII) and the depsides by (LXIII). Depsidones never have hydroxyl/methoxyl groups ortho or para to ether linkage in ring A, but there is always one of these groups in these positions in ring B.

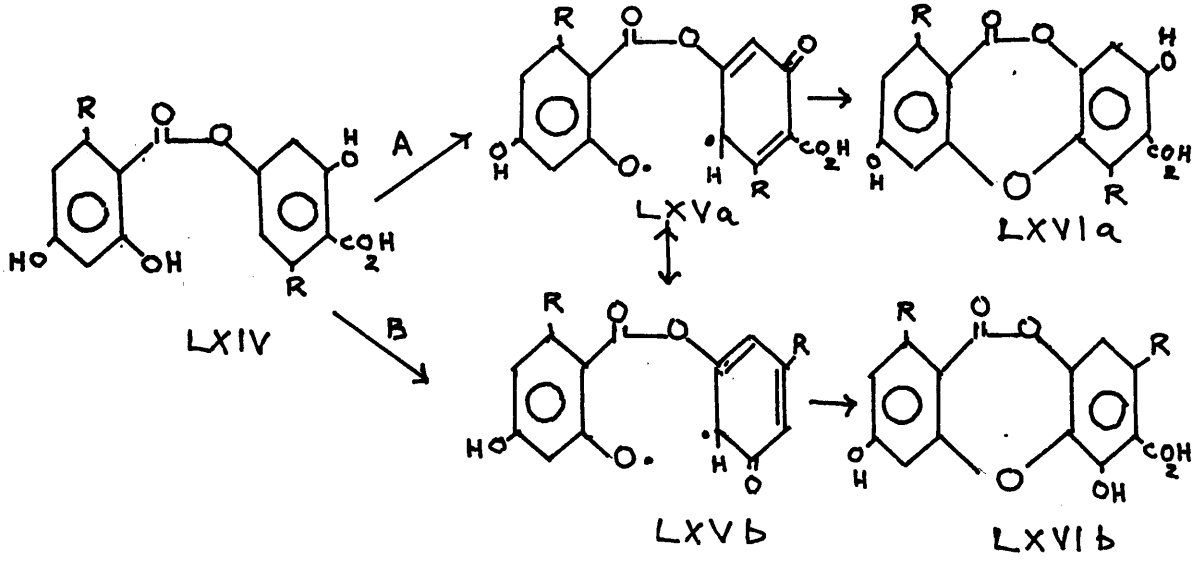


LXII

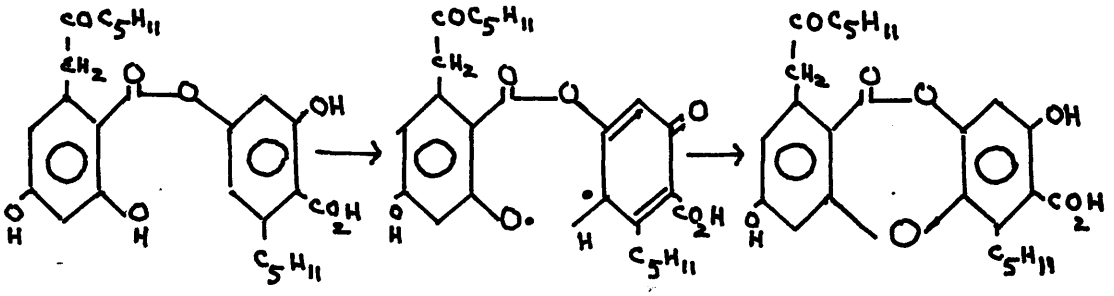


LXIII

The biogenetic relationship between depsides and depsidones has been stressed by Asahina [38] who considered that depsidones were derived in Nature from hydroxylated depsides by dehydration [36]. However, it seems much more likely mechanistically that the biogenesis of depsidones involves the oxidative phenol coupling of depsides [3], [4], [38]. Thus the depside (LXIV) can give rise to depsidones, (LXVIa) and/or (LXVIb) through intermediate biradicals (LXVa) or (LXVb).



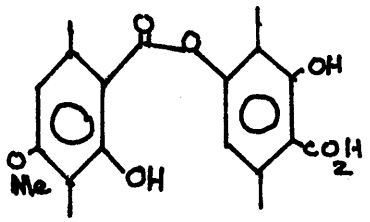
This biogenetic scheme finds its support in the occurrance of depsidones and closely related depsides.within separate varieties of a single species. Thus, the depsidone physodic acid (LXVIII) is present in all the ten closely related species of the genus Parmelia. However, two "chemical strains" of P. furfuraceae [40], [41] are known one of which, namely, v. olivetorina (Zopf.) (Zahl.) lacks physodic acid but contains the depside olivetoric acid (LXVII) [42], the supposed biogenetic precursor of physodic acid. It seems reasonable to assume that a dehydrogenating system common to most members of this group of Parmelia is deficient or lacking in the variety olivetorina [43].



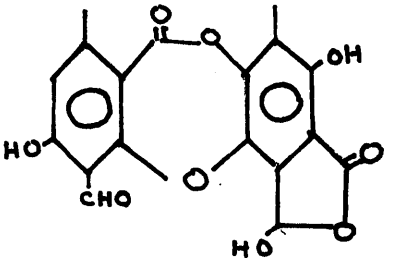
LXVII LXVIII

Similar relationships have been observed by Runemark [42] in the European yellow Rhizocarpon species. Most of the species contain the related depsidones psoromic acid (LXXII), stictic acid (LXXI) and norstictic acid (LXX). However, Rh. lindsayanum Räs. is represented

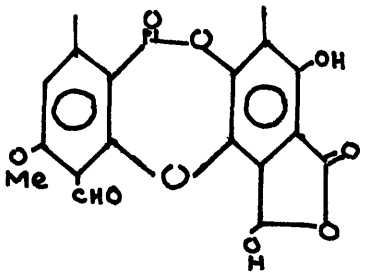
by two "chemical strains" containing psoromic acid (LXXII) and the supposed precursor depside barbatic acid (LXIX) respectively. The accumulation of barbatic acid probably indicates a block in a dehydrogenating system [43].



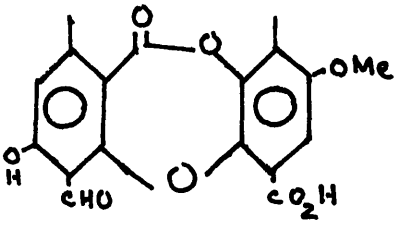
LXIX



LXX

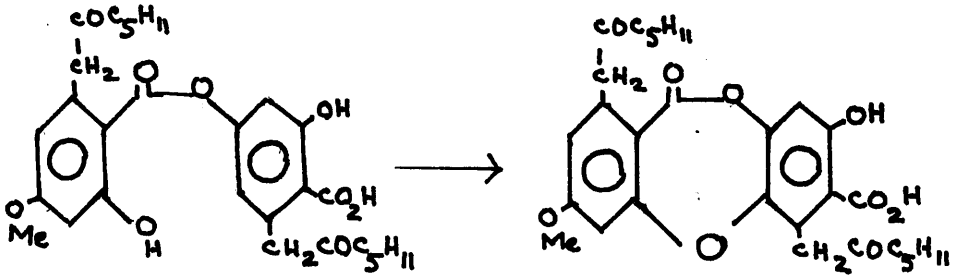


LXXI



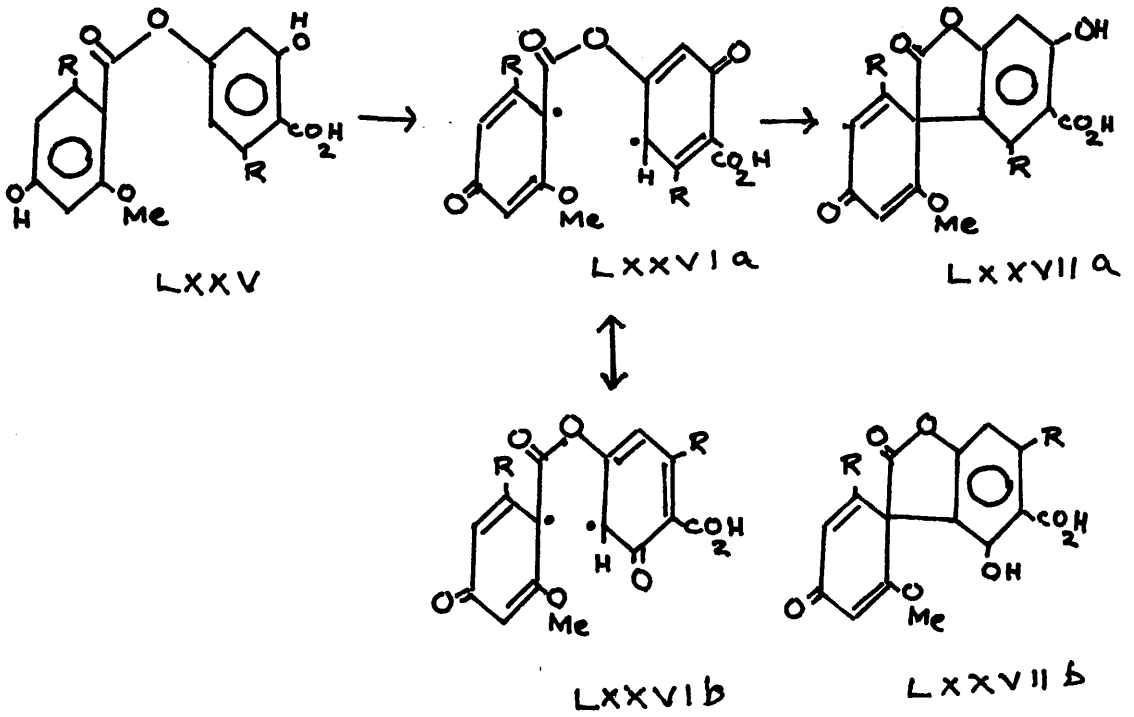
LXXII

Again, there is a similar relationship between microphyllic acid (LXXIII) and α-collatolic acid (LXXIV), both of which occur in 'cetraria collata microphyllina' and 'cetraria collata' respectively.



LXXIII LXXIV

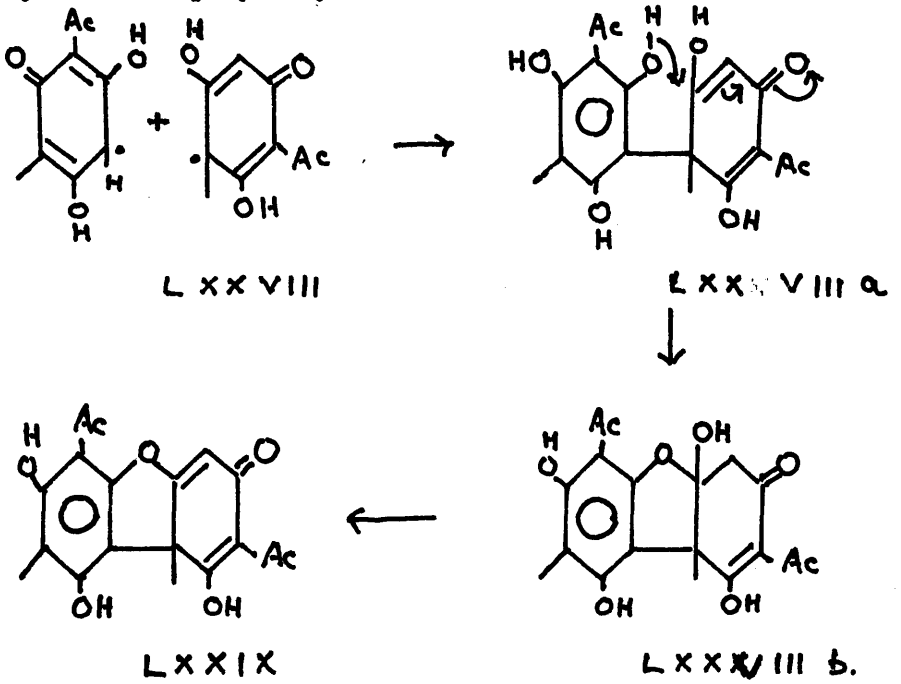
Erdtman and Wachtmeister [44], [45] have recently shown the existence of another class of lichen substances, represented by picrolichenic acid [45] (LXXVIIa: R = n-C_5H_{11}), presumably formed in Nature by intramolecular oxidative carbon-carbon coupling of a depside and gave the name "depsone" to this class. As suggested by Wachtmeister [43], [45], a depside (LXXV) containing a free hydroxyl group in the para position and a methoxyl group (or a hydroxyl group protected in some other way) in the ortho position to the ester bridge would give a mesomeric diradical (LXXVIa) ↔ (LXXVIb) and thence by coupling the γ-lactones (LXXVIIa) and (LXXVIIb):



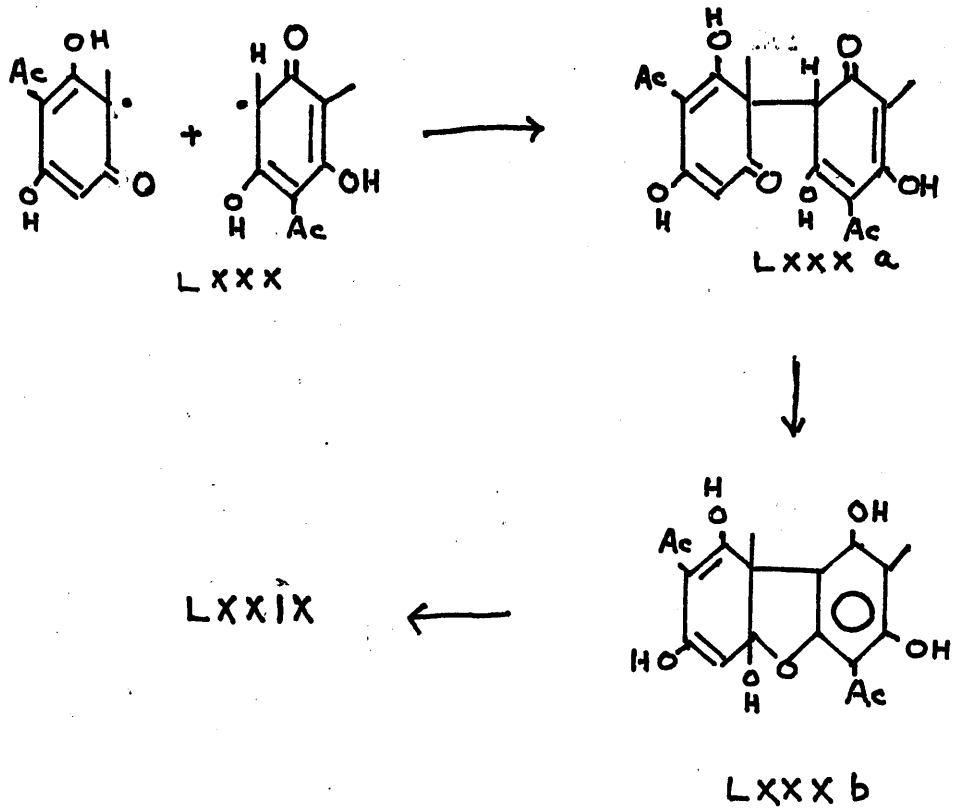
Picrolichenic acid (LXXVIIa: R = n-C_5H_{11}) can obviously be considered to have been formed in Nature by the intramolecular oxidative coupling of a hypothetic "iso-perlatolinic acid" (LXXV; R = n-C_5H_{11}).

Another class of lichen substances which is surely derived in Nature by phenol coupling is the group based on dibenzofuran. The most important of these lichen substances is usnic acid (LXXIX) [46]. It has long been appreciated [46], [47] that usnic acid is built up in Nature from two molecules of C-methylphloroacetophenone by oxidative coupling. However, Barton, Deflorin and Edwards [48] were only

recently successful in first accomplishing an elegant two step synthesis of usnic acid, from C-methylphloroacetophenone by the action of alkaline potassium ferricyanide as outlined in the scheme (LXXVIII) → (LXXIX) (see below). There can be little doubt that this is the mode of synthesis employed by Nature herself.

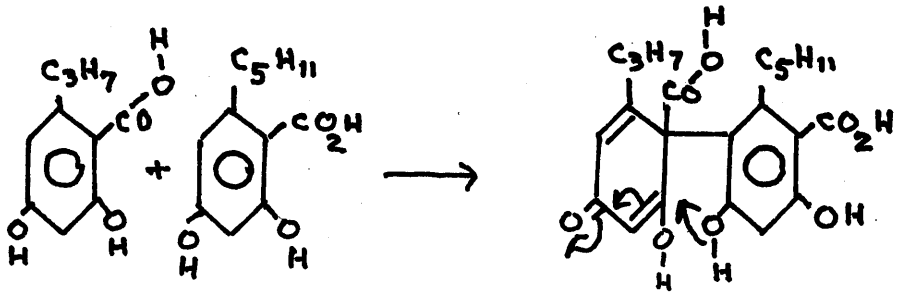


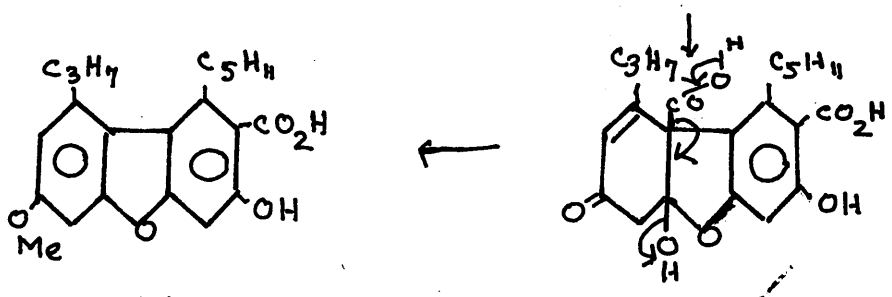
Wachtmeister [43] while agreeing with the general biogenetic scheme given above has given a somewhat different interpretation of the reactions involved in the synthesis of usnic acid, as indicated below (LXXX) → (LXXIX):



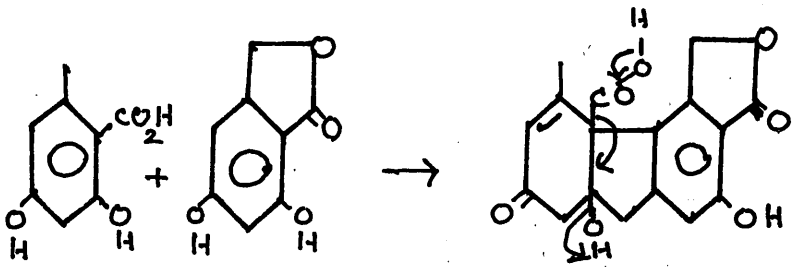
However, this does not alter the importance of phenol coupling in the biosynthesis of usnic acid.

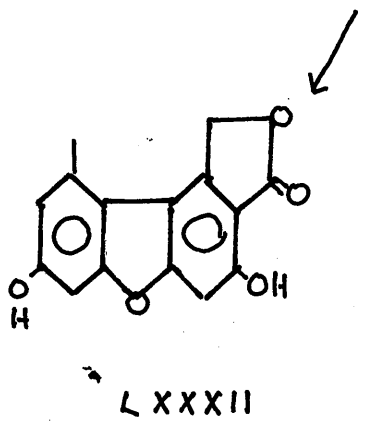
Similar schemes have been indicated for the biogenesis of the fully aromatic dibenzofuran lichen substances, didymic acid (LXXXI) [49] and strepsilin (LXXXII) [50].





LXXXI

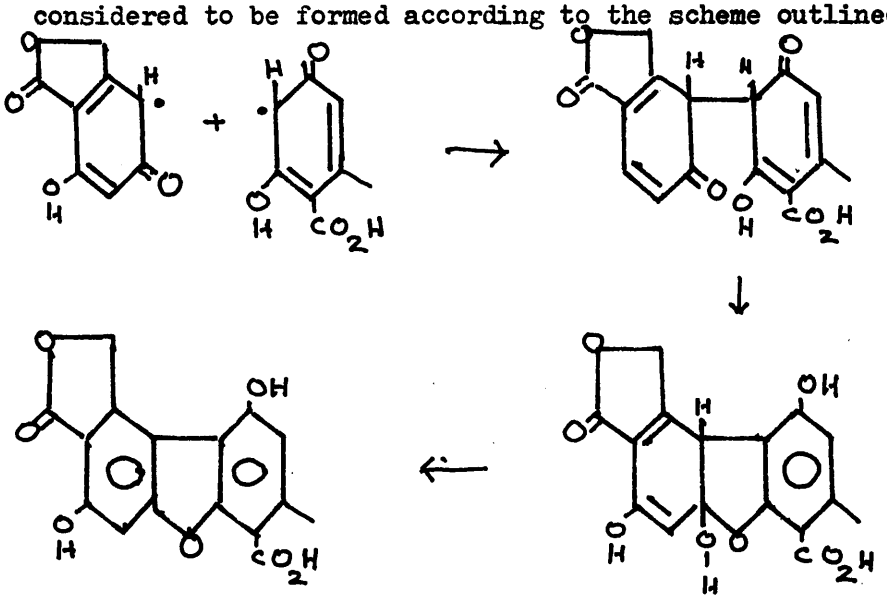




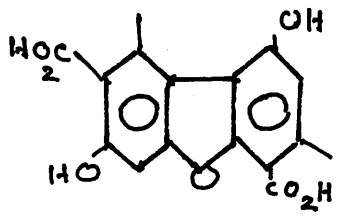
LXXXII

Wachtmeister [43] has again commented on the types of radicals that are most likely to be involved in the biogenesis of didymic acid and strepsilin.

Similarly porphyrilic acid (LXXXIII) [51], [52], [53] is considered to be formed according to the scheme outlined below [43]:-



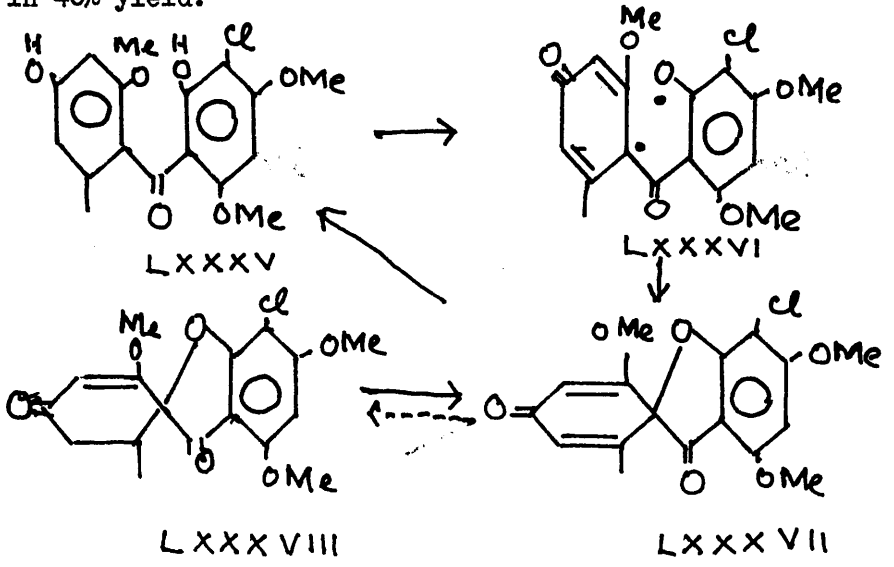
LXXXIII



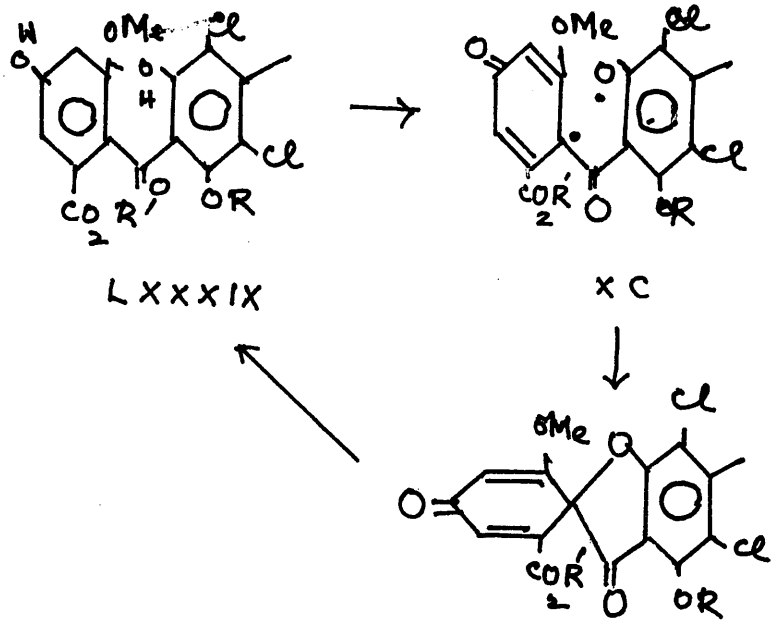
LXXXIV

Pannaric acid (LXXXIV) [54], [55], [43], the lichen acid from Crocynia membranacea (Dicks.) Zahlbr., must also have a similar biogenetic origin.

The physiologically active mould metabolite griseofulvin, isolated by Oxford, Raistrick and Simonart [56], has been assigned the structure (LXXXVIII) [57]. The bromo-analogue [58] and the halogen free compound [59] have also been obtained as fungal metabolites. Birch et al. [60] have shown recently that the biogenesis of griseofulvin (LXXXVIII) conforms to the 'acetate' hypothesis [61]. However, Barton and Cohen [3] had suggested that the biogenesis of griseofulvin (LXXXVIII) follows the usual poly-β-diketone [62], [63] pattern only as far as the hydroxylated benzophenone stage (LXXXV) while the final spirane formation is effected by phenol coupling of (LXXXV). This latter view has now been supported by the observations of Scott [64] who has successfully oxidised (LXXXV) with alkaline potassium ferricyanide to dehydrogriseofulvin (LXXXVII) in 40% yield.



The fungal metabolites geodin and erdin, isolated by Raistrick and Smith [65] from Aspergillus terreus Thom., have recently been shown by Barton and Scott [66] to have the structures (XCl) and (XCll) respectively. These metabolites could also be derived from the approximately substituted hydroxylated benzophenone (LXXXIX) via (XC), and Scott [64] has recently synthesised (±)-geodin methyl ether (XCl: R = R' = Me) in 33% yield, from the hydroxylated benzophenone (LXXXIX: R = R' = Me) by the action of alkaline ferricyanide, thereby lending further support to the hypothesis of oxidative phenol coupling.



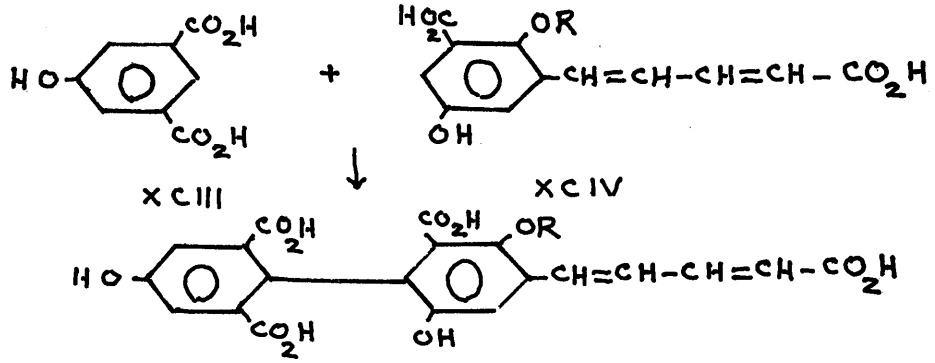
LXXXIX

XC

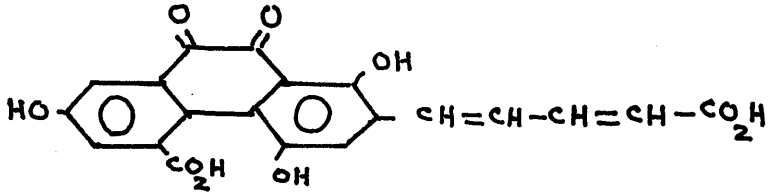
XCl: R = H; R' = Me

XCII: R = R' = H

The fungal pigment thelephoric acid (XCV) [67] can be derived by a phenol coupling step from the two phenolic precursors (XCIII) and (XCIV) as shown below [3]:

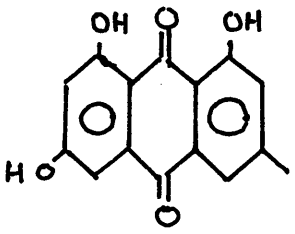


XCIII + XCIV

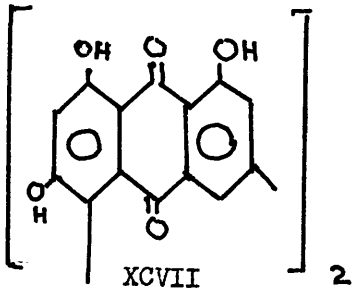


XCV

The colouring matter skyrin [68], [69] has been assigned the structure (XCVII) [70] and it can obviously be built up from two molecules of (XCVI) by phenol coupling [3], [70b].

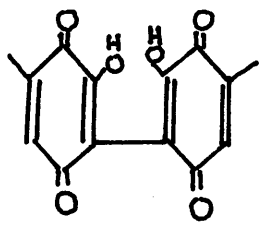


XCVI

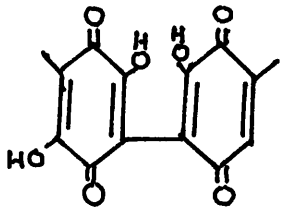


XCVII 2

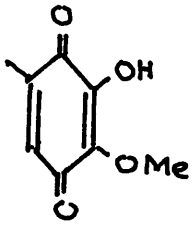
The symmetrical nature of the fungal metabolites phoenicin (XCVIII) [71] and oosporein (XCIX) [72], [73], together with the formation of the structurally related fumigatin (C) [74] and spinulosin (CI) [75] seems to suggest that the biosynthesis of phoenicin and oosporein probably involves oxidative coupling at some stage.



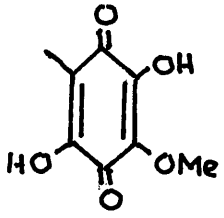
XCVIII



XCIX



C

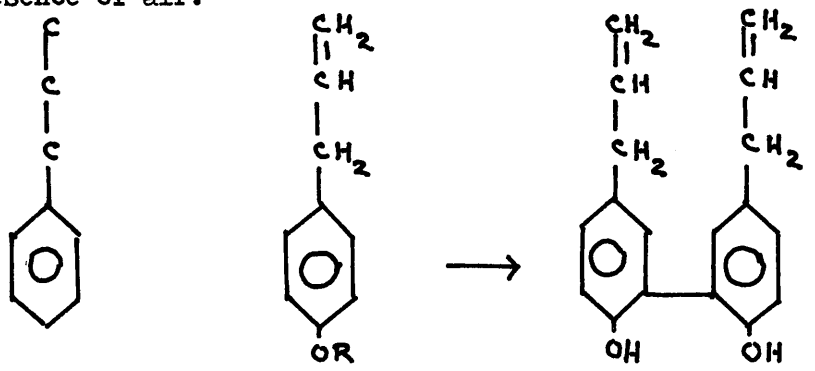


CI

LIGNANS and Related Compounds (The C_6 - C_3 Group).

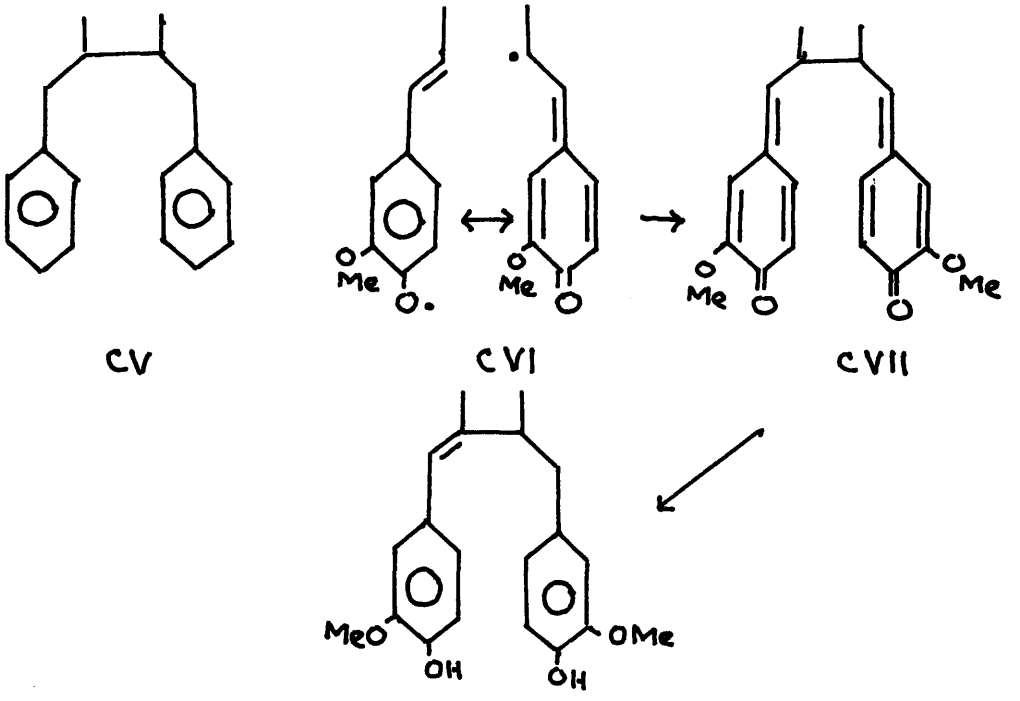
There is a vast number of natural products which contain the so-called C_6-C_3 structural unit (XII) [76]. It has been suggested that such compounds based on polymerised C_6-C_3 units have been derived by phenol coupling. Magnalol (CIV) [77] is the simplest case of this type which occurs in the bark of some magnolia species.

Significantly, chavicol methyl ether (CIII; R = Me) [78] has been found to occur in other species of the same genus. The obvious biogenetic relationship between magnalol and chavicol already pointed out by Barton and Cohen [3] has recently been substantiated by Erdtman and Runeberg [79] when they synthesised magnalol (CIV) from chavicol (CIII; R = H) by oxidation with ferric chloride in the presence of air.

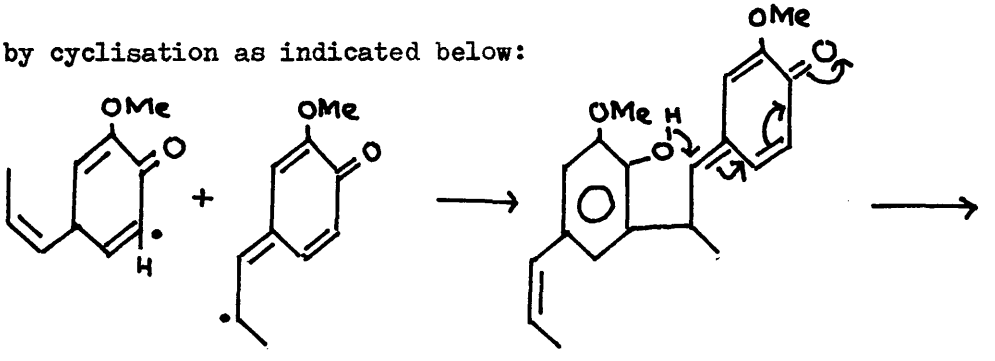


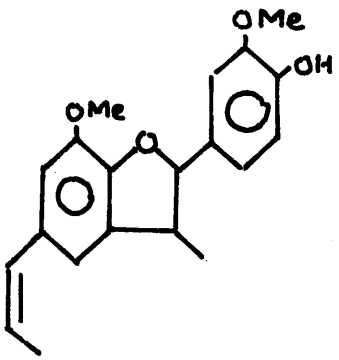
(CII) CIII CIV

The most important group of $C_6 - C_3$ compounds is the class of natural products known as lignans [2], [80]. Lignans [2] are composed of two $C_6 - C_3$ units coupled in the β-positions (CV). All lignans have phenolic hydroxyls (or derived ether groups) in the para-positions , and their biogenesis resulting from the coupling of two phenol radicals has already been clearly pointed out by Erdtman [81], [82], [83]. Thus, guaiaretic acid (CVIII) [81], [82], [83], [84] may be regarded to have been formed from isoeugenol as indicated below: (CVI → CVIII)

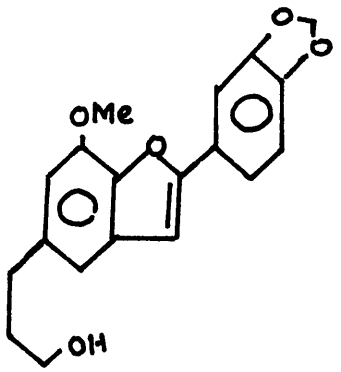


Actually, the oxidation of isoeugenol by ferric chloride yields dehydrodiisoeugenol (CIX) [81], [82] and dehydroguaiaretic acid (CX) [85]. While dehydrodiisoeugenol (CIX) is possibly derived by ortho-β-coupling followed by addition of the phenolic hydroxyl to the enone system, dehydroguaiaretic acid is formed by β-β coupling followed by cyclisation as indicated below:

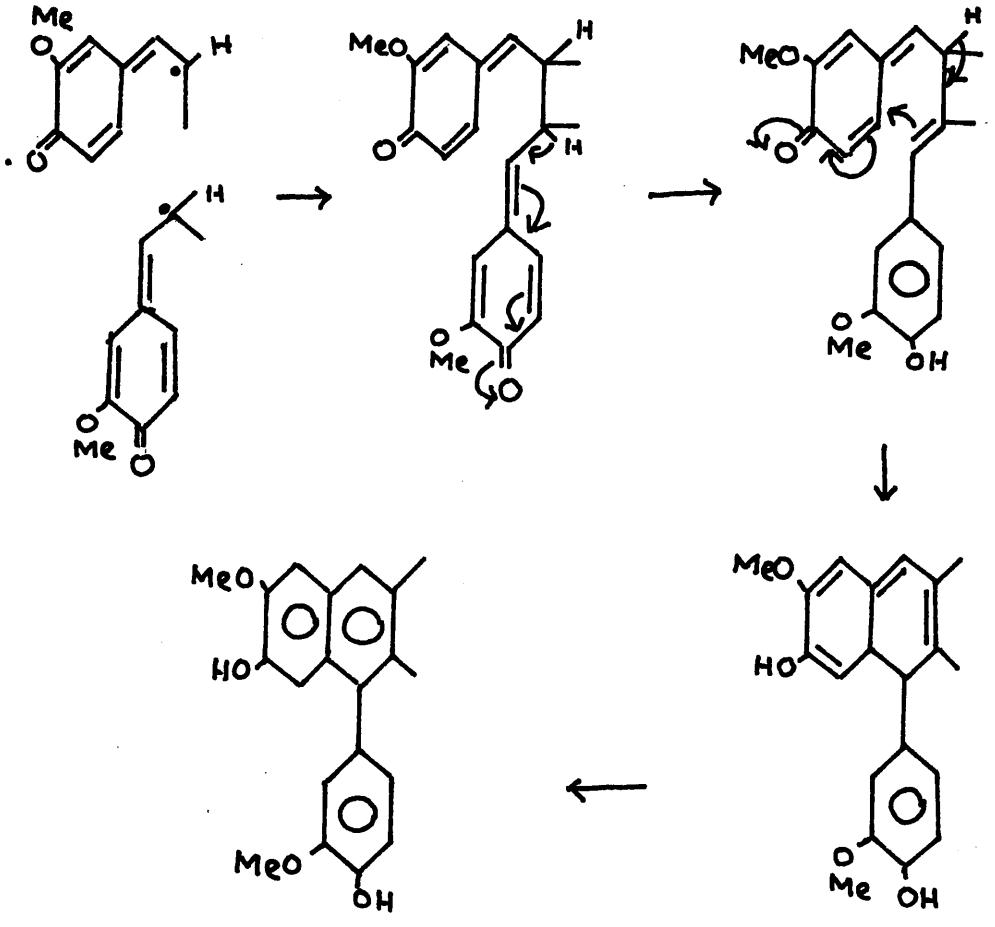



OMe
OH
OMe
O

CIX


O
O
OMe
O
OH

CIXa

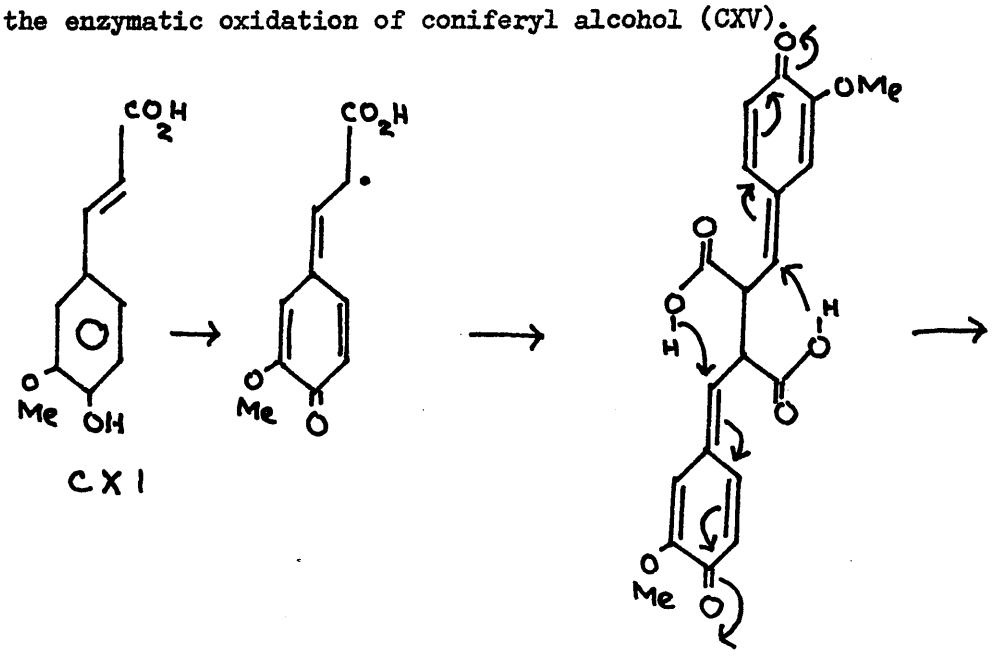

Me
O
H
O
H
O
Me
O
MeO
H
O
H
O
Me
O
MeO
H
O
Me
OH
MeO
HO
MeO
OH
MeO
HO
O
Me
OH

CX

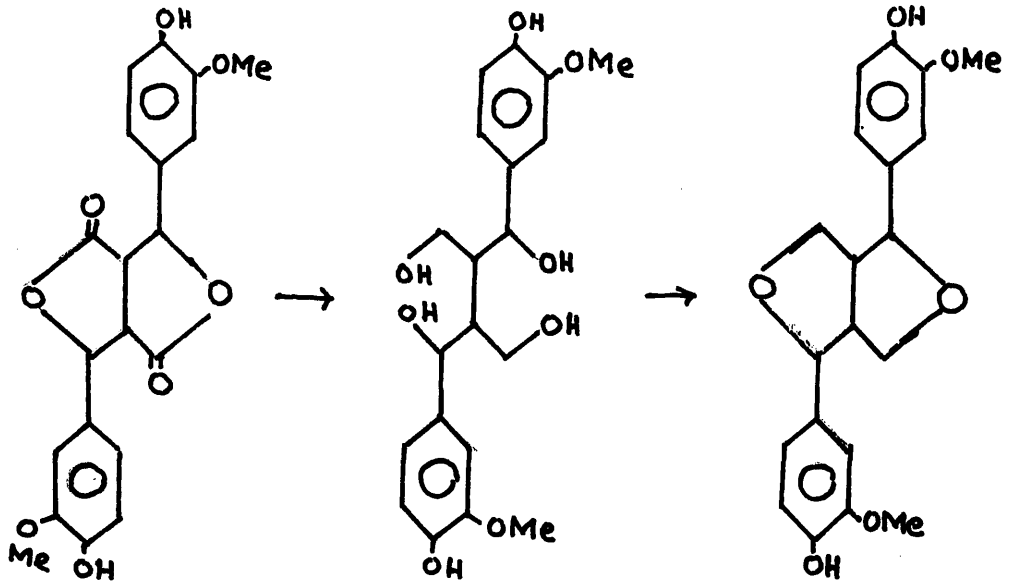
It is interesting to note that a compound similar to dehydrodiisoeugenol (ClX), 'egonol' (ClXa) has since been isolated from the fruits of styrax japonicum and its genesis probably follows the same course as shown above for dehydrodiisoeugenol.

Ferulic acid (CXl) yields on oxidation a dilactone, dehydrodiferulic acid (CXll) [87], [88] and obviously it is formed by β:β-coupling. (±)-Pinoresinol (CXIV) [89] has been further obtained from dehydrodiferulic acid via the tetrol (CXlll) obtained by the lithium aluminium hydride reduction of the dilactone (CXll). The (±)-pinoresinol is one of the most important of the naturally occurring lignans.

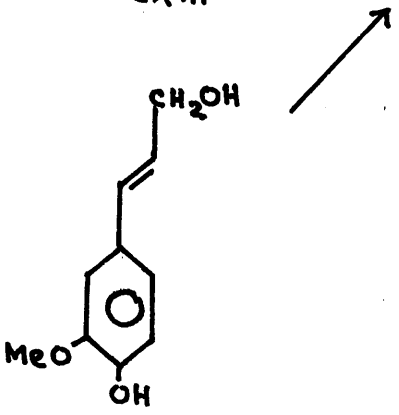
(±)-Pinoresinol has also been obtained [90] directly by the enzymatic oxidation of coniferyl alcohol (CXV).



CXI



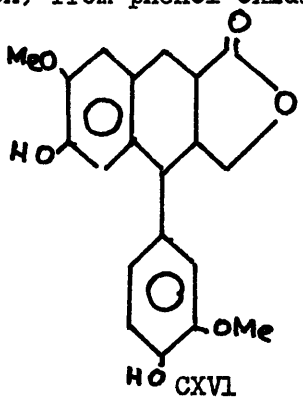
CXII CXIII CXIV



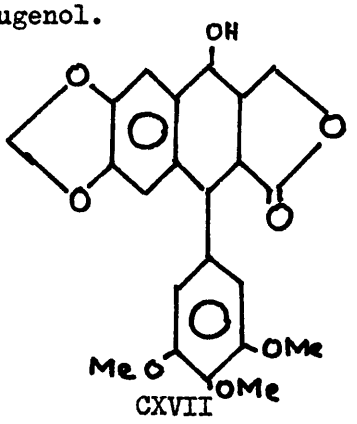
CXV

There is a further major group of lignans represented by conidendrin (CXVI) [91] and podophyllotoxin (CXVII) [92] which has an additional carbon-carbon bond between the α-position of one unit and the aromatic nucleus of the other. The biogenesis of

these compounds can also be accommodated within this general scheme [3] if we assume that first of all, as in the case of other lignans, there is a β:β-coupling and this is followed by a further bond formation as in the scheme above for the genesis of dehydrodiguaiaretic acid (CX) from phenol oxidation of isoeugenol.



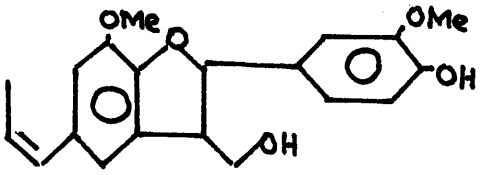
CXVI



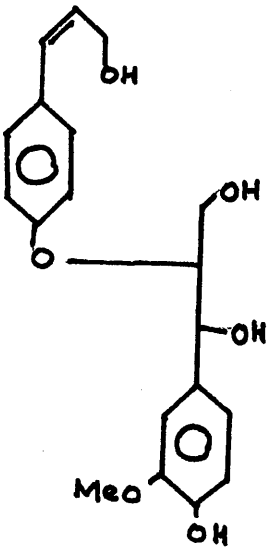
CXVII

It had been suggested quite early by Klason [93] that lignin is a dehydrogenation product of coniferyl alcohol (CXV). Erdtman [81], [82], [83], [94] and Haworth [2] elaborated this view further. More recent brilliant studies of Freudenberg and his co-workers on the enzymatic oxidation of coniferyl alcohol and analogous phenyl propanes have lent further support to the essential correctness of this view. They have been successful in isolating the dehydrodiisoeugenol analogue (CXVIII; cf CIX) [95], (±)-pinoresinol (CXIV) [90], the ether (CXIX) and dehydroconiferyl alcohol (CXX). Freudenberg [96] believes that coniferyl alcohol is the primary building unit in the

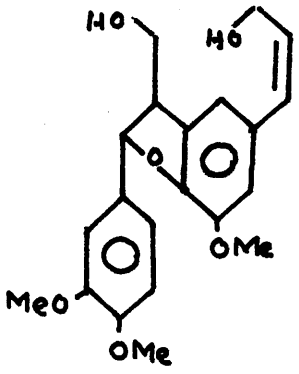
biosynthesis of lignin, while (CXIV), (CXVIII), (CXIX) and (CXX) are also incorporated to a secondary extent.



CXVIII



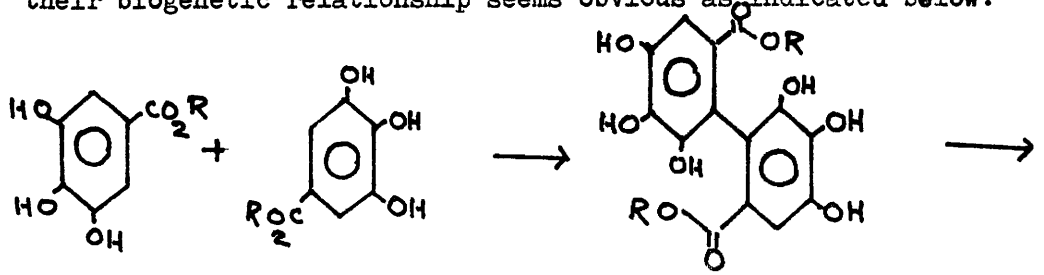
CXIX



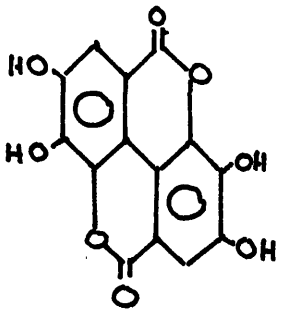
CXX

TANNINS

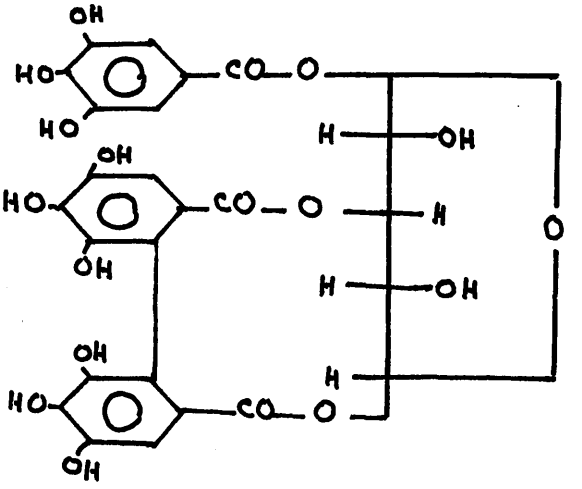
Ellagic acid (CXXIII) and gallic acid (CXXI; R = H) occur together in Coriaria japonica [97] as well as in other species and their biogenetic relationship seems obvious as indicated below:



CXXI CXXII



CXXIII

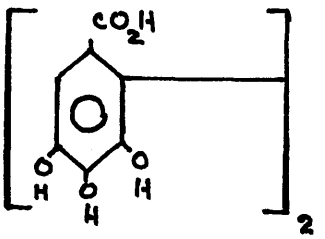


CXXIV

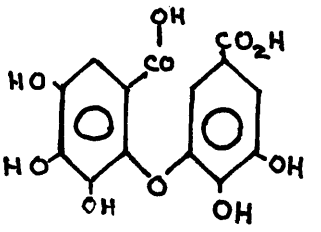
'In vitro' experiments to oxidise gallic acid to ellagic acid, however, revealed that methyl gallate (CXXI; R = Me) but not gallic acid, was dehydrogenated to ellagic acid [98], [99]. This oxidative dimerisation presumably proceeds through the intermediate dimethylhexahydroxydiphenate (CXXII; R = Me) which rapidly undergoes intramolecular trans-esterification to afford ellagic acid. It is, therefore, probable that ellagic acid is formed in Nature from gallic acid esters, e.g. sugar gallates, and this conclusion finds ample support

in the recent work of Schmidt and his co-workers [100] on corilagin (CXXIV) which is a cyclic diester (optically active) of hexahydroxy-diphenic acid.

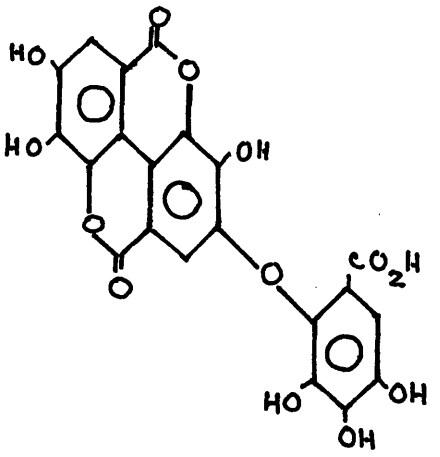
Among the other acids, isolated in the recent studies of Schmidt and his co-workers [100], that are possibly involved in the building up of tannin molecules are (CXXV), dehydrodigallic acid (CXXVI) and valonea acid (CXXVII) and their obvious genesis from gallic acid by oxidative phenol coupling needs no further comment.



CXXV



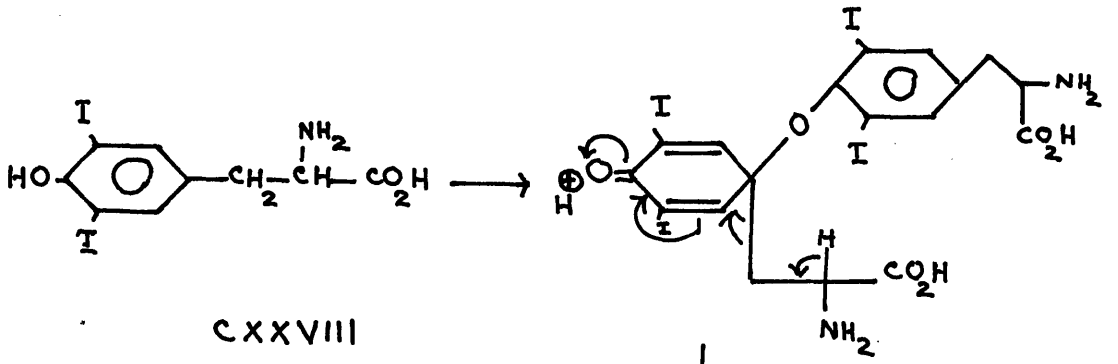
CXXVI



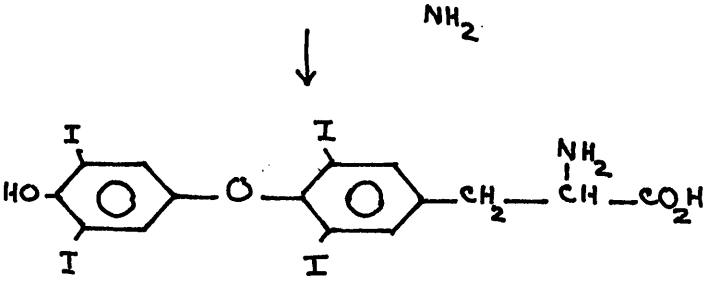
CXXVII

Miscellaneous Natural Products.

The biogenetic pathway for thyroxine (CXXIX) [101], [102], [103] most probably involves the oxidative coupling of 3:5-diiodotyrosine (CXXVIII) and this synthesis has actually been accomplished [104], though in a poor yield, in vitro.

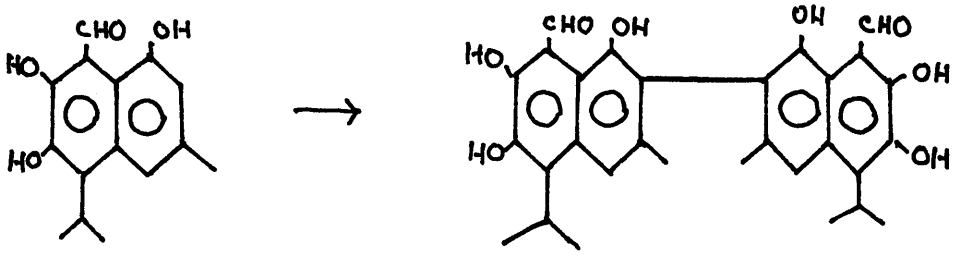


CXXVIII



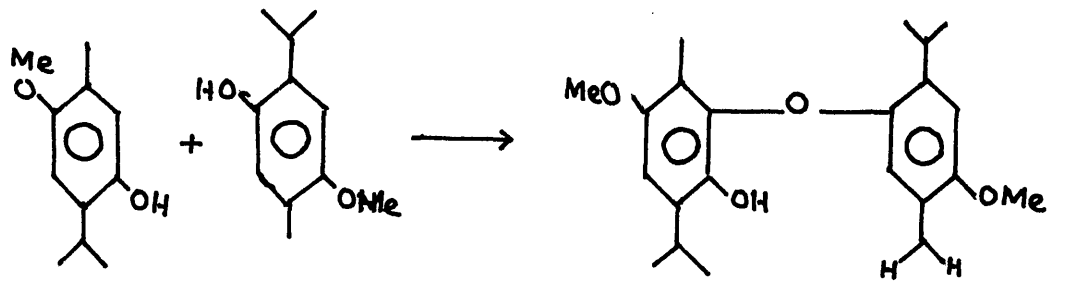
CXXIX

Gossypol (CXXX) [105], the pigment of the cotton seed, is possibly formed from two identical sesquiterpenoid moieties by phenol coupling [3], [4].



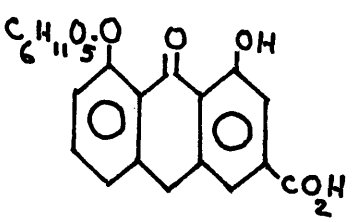
CXXX

Libocedrol (CXXXII) occurs along with p-methoxythymol (CXXXI) in the heartwood of the incense-cedar and their biogenetic relationship seems obvious [3], [4].

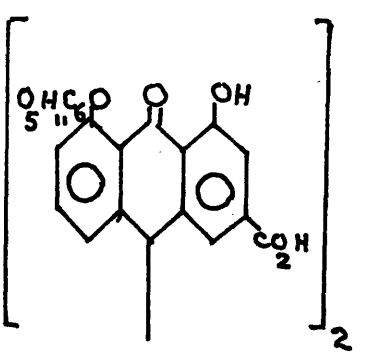


CXXXI CXXXII

The sennosides A and B, stereoisomers of constitution (CXXXIV) [107], [108], are present in Folia sennae. Stoll and his collaborators have also accomplished an elegant synthesis of these compounds by the phenol coupling of glucoside-rheinanthrone (CXXIII). The biogenetic significance of this synthesis has been commented upon by Stoll.

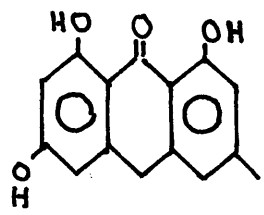


CXXXIII

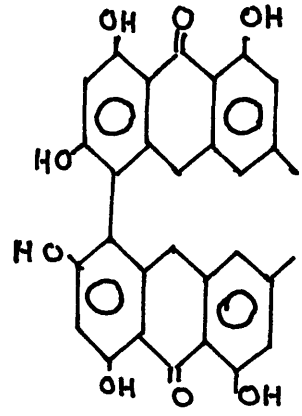


CXXXIV

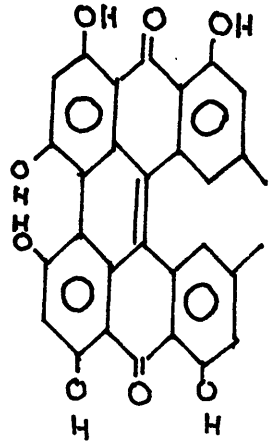
The photodynamic pigment of St. John's wort, hypericin has been assigned the constitution (CXXXVIII) by Brockmann and his collaborators [109]. Protohypericin (CXXXVII) also occurs along with hypericin in Nature and is transformed into the latter on irradiation. Protohypericin itself has been synthesised from emodin anthrone (CXXXV) by phenol coupling [110], [111], [112]. Most probably this represents the true path of the biosynthesis of hypericin. It may be noted that the fungal metabolite penicillopsin (CXXXVI) [111] probably represents the first step in the biosynthesis.



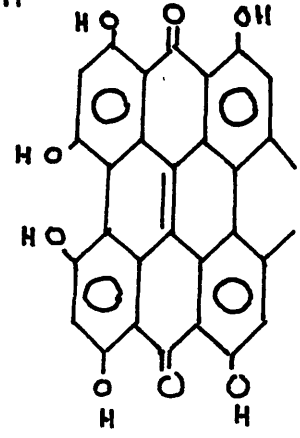
CXXXV



CXXXVI



CXXXVII



CXXXVIII

The enzymatic oxidation of phenols has already been referred to in Chapter I and there are sufficient reasons to believe that the enzymatic oxidation of phenols is also free radical in character [114] and leads to qualitatively similar products as are obtained in the oxidations with inorganic reagents.

The foregoing account gives a fairly cross-sectional, though by no means exhaustive, presentation of the biogenetic importance of the reaction mechanism - the coupling of phenol radicals.

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A REVIEW OF THE RELEVANT ASPECTS OF THE CHEMISTRY OF MORPHINE AND APORPHINE ALKALOIDS.

It has been explained at length elsewhere that the object of the present work has been to study the reaction mechanism 'oxidative coupling of phenols', especially with a view to synthesise 'in vitro' the alkaloids of morphine and aporphine type. It will, therefore, be pertinent to consider briefly the chemistry of these two types of alkaloids.

Alkaloids of the Morphine Group.

The morphine alkaloids have been the subject of most extensive study ever since morphine, the principal alkaloid of this group, was isolated by Sertürner in 1805. The remarkable analgesic properties of morphine and many of its derivatives and the fundamental importance of the wide variety of molecular rearrangements undergone by these alkaloids account for the exceptionally long chapter on the chemistry of morphine alkaloids in the history of natural products.

This group is composed of five closely related alkaloids, morphine, codeine, neopine, thebaine and oripavine, and two bases of a somewhat different type, sinomenine and hasubanonine.

Elucidation of the Structure of Morphine, Codeine and Thebaine.

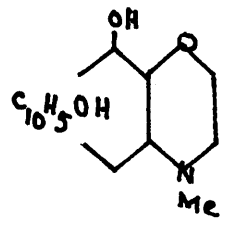
The close relationship between morphine, codeine and thebaine became clear fairly early after their compositions $C_{17}H_{19}O_3N$, $C_{18}H_{21}O_3N$ and $C_{19}H_{21}O_3N$ respectively were established by 1852. Morphine is a phenol and can be methylated easily to give codeine. Moreover, both morphine and codeine were shown to contain a secondary alcoholic group by the usual methods. Codeine was readily oxidised to a ketone, codeinone, which is also obtained by the acid hydrolysis of thebaine. Therefore, thebaine is simply the methyl ether of the enolic form of codeinone.

The nature of the third oxygen atom in these was soon recognised as part of an ether type linkage. Possible presence of a phenanthrene skeleton, probably partially hydrogenated, was indicated by several reactions, although quite drastic in nature. While morphine and codeine contain an isolated ethylenic double bond (bromine water decolorisation, reduction to dihydro derivatives, and careful oxidation by potassium permanganate to a dihydroxydihydrocodeine), thebaine contains two double bonds in conjugation (maleic anhydride or p-benzoquinone adducts).

The mode of linkage of the nitrogen atom was demonstrated by exhaustive methylation. Although this method of degradation did not

yield any useful results in the case of morphine due to the formation of a phenol betaine, codeine methiodide afforded a base, α-codeimethine, showing thereby that nitrogen in codeine forms part of a ring. α-Codeimethine on treatment with alkali suffers a double bond shift and is isomerised to β-codeimethine. Further degradation of α- or β-codeimethine resulted in complete loss of the basic side chain and gave a fully aromatic phenanthrene derivative. Similar results were obtained by the 'acetolysis' of morphine and thebaine methiodides. All the foregoing results seemed to suggest that in codeine one NMe group and two carbon atoms were in some way attached to a partially hydrogenated phenanthrene skeleton.

Frequent formation of β-dimethylaminoethanol during aromatizing degradations had led Knorr [1] to propose various ozazine formulae (I), (II) for morphine in the early stages of this field. He explained the formation of dimethylaminoethanol due to hydrolytic scission of an oxazine system.



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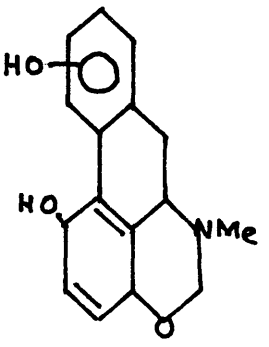

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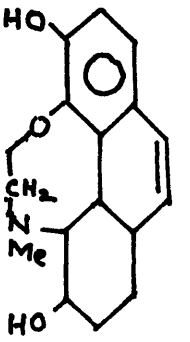
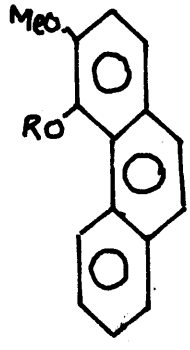


III

However, Pschorr et al. [2] were able to demonstrate the presence of oxygen substituents at positions 3:4 and 6 of phenanthrene system in morphine. Consequently, Knorr [3] modified his oxazine formula (II) for morphine to (III). Even then, (III) could not stand the rigours of experimental evidence and was finally abandoned when it was discovered that metathebainone in which the function of all the three oxygen atoms was known, (one OMe, one phenolic -OH and one -C=O) gave dimethylmorphol (IV; R = Me) and β-dimethylaminoethanol on exhaustive methylation and acetolysis, indicating that the latter could arise by scission of a carbon-carbon link [4].

Vongerichten and Pschorr showed by their work on morphenol (V; R = H) obtained as methyl ether by the exhaustive methylation of codeine) that the morphine alkaloids were derivatives of 3:6-dihydroxy-4:5-phenanthrylene oxide (VI) [5].



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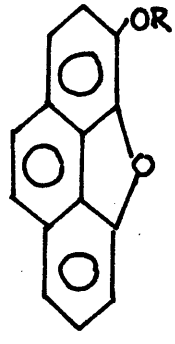

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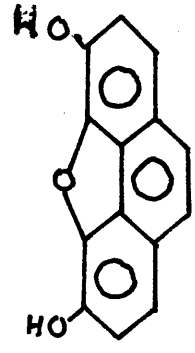
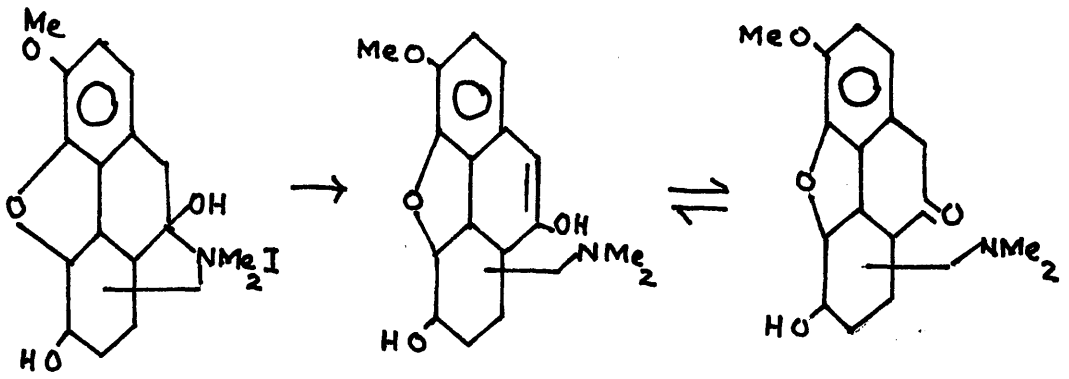


VI

Several other formulae for morphine were suggested in the meantime but none of them survived the rigours of experimental data for long and were dismissed one after the other.

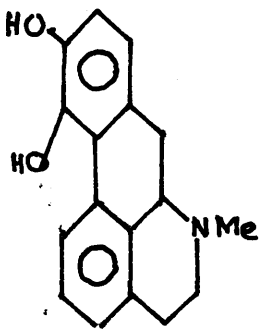
Codeine was oxidised with chromic acid to give hydroxycodeine. Hofmann degradation of this hydroxy codeine furnished a ketocodeimethine in which the oxygen appears as a carbonyl group, and this was degraded by acetic anhydride to a methoxydiacetoxyphenanthrene that loses an acetoxy group on oxidation to a quinone. The new acetoxy group and hence the new hydroxyl group in hydroxycodeine must, therefore, be at position 9 or 10, and since this group is converted into a carbonyl group during Hofmann degradation, a double bond must be introduced at position 9, 10 during scission of the nitrogen ring.



VII VIII IX

This established the point of linkage of nitrogen at C-9 or C-10, although the precise point of attachment was established only by the ultimate synthesis of morphine skeleton. The point of attachment of the carbon end of the side chain, however, remained a mystery for many years.

The formation of apomorphine (X) by the acid treatment of morphine led Pschorr [6] to suggest the isoquinoline formula (XI) for morphine. However, Knorr modified this structure to (XII) as the methine base derived from hydroxycodeine was not a naphthol. Also, (XII) could explain the α-β-codeimethine isomerisation as involving the migration of the double bond from its position in (XII) to that in (XI).



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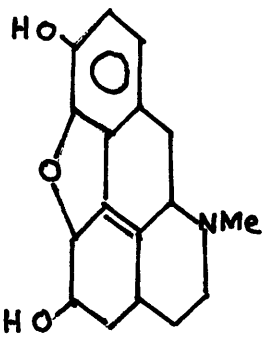
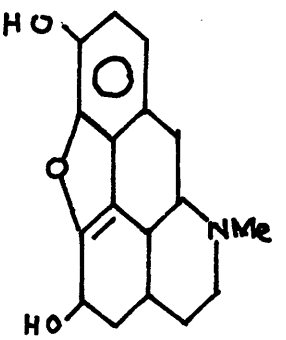


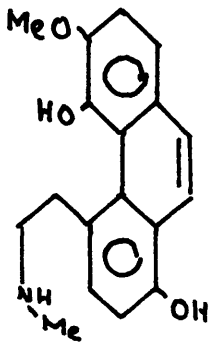
XI



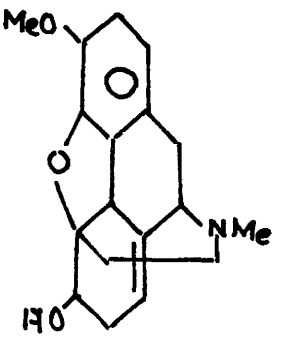
XII

However, the possibility of the C-8 attachment of the carbon end of nitrogen-containing side chain was eliminated by a study of isomeric codeines, isocodeine, ψ-codeine and allo- ψ-codeine obtained by the hydrolysis of halogenocodides. Codeine and isocodeine differ only in the steric arrangement of the -CH(OH)- group as they furnish the same codeinone on oxidation. ψ-Codeine and allo- ψ-codeine comprise another epimeric pair giving the same ψ-codeinone on oxidation. While codeinone on 'acetolysis', yielded 3-methoxy-4:6-diacetoxy-phenanthrene, a similar degradation of ψ-codeinone afforded 3-methoxy-4:8-diacetoxyphenanthrene, obviously meaning that both the C-6 and C-8 positions in codeine must be free from other substituents and consequently the formulae (XI) or (XII) for morphine were untenable.

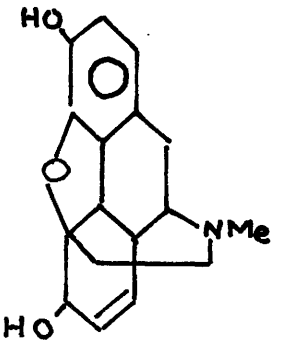
The fact that thebenine (XIII), a rearrangement product of thebaine, still contained the side chain attached to the phenanthrene nucleus at C-5 led Knorr and Hörlein [7] to propose the formula (XIV) involving a 9:5-oxide bridge for codeine. This formulation



XIII



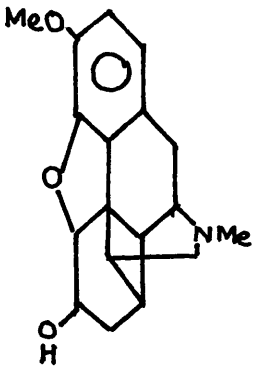
XIV



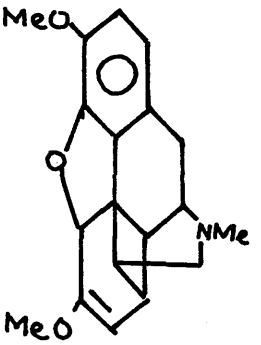
XV

would explain the α:β-codeimethine isomerisation as involving a shift of the double bond from 8:14 position to 13:14 position, although β-codeimethine, on hydrogenation, did not behave as a fully aromatic naphthalene derivative. (XIV) was accordingly modified by Wieland and Koraleck [8] to (XV). In the meanwhile several other formulations involving a cyclopropane ring, or a 'camphane' structure, or a '4:8' oxide bridge etc., were put forward but none of them explained all the observed facts satisfactorily.

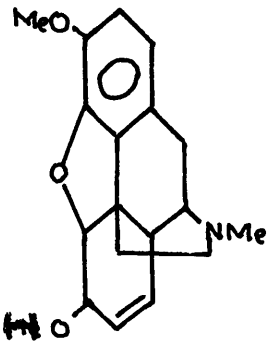
Gulland and Robinson [9] proposed the attachment of the side chain at an angular position so that its extrusion was a necessary part of aromatisation and of the two possible positions, C-13 was selected. Accordingly they proposed the 'camphane' formulae (XVI) and (XVII) for codeine and thebaine respectively. These were subsequently modified to (XVIII) and (XIX) by the same authors [10] on the basis of their work on 14-hydroxycodeinone which was obtained by the action of perhydrol on thebaine and is formed presumably by the 1:4-addition of hydrogen peroxide followed by the hydrolysis of the resulting hemiacetal.



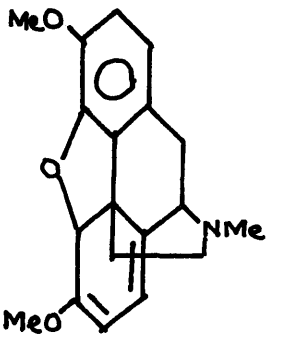
XVI



XVII

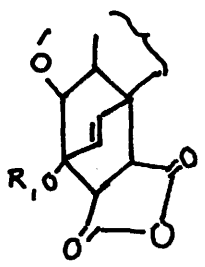


XVIII

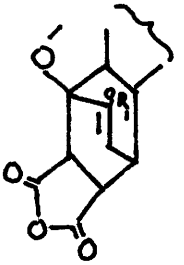


XIX

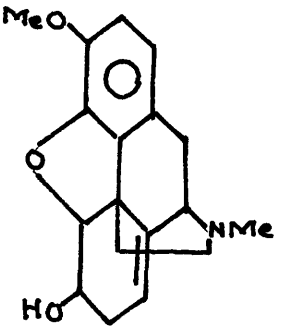
The alloted arrangement of the conjugated double bonds in thebaine (XIX) was supported by the fact that the maleic anhydride adduct (XX) could not be hydrolysed to a ketone [11]. The alternative arrangement on the other hand, would yield an adduct which is an enol ether (XXI) and would afford a ketone on hydrolysis.



XX



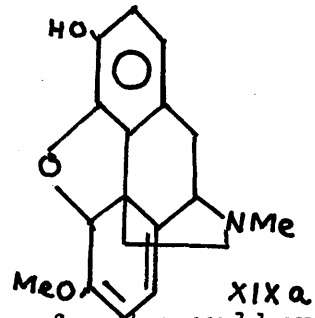
XXI



XXII

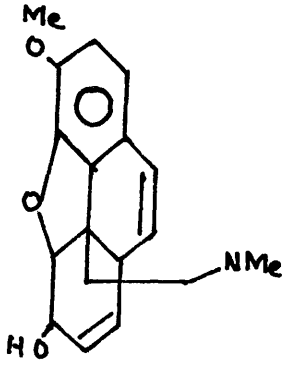
Neopine, another member of this group of morphine alkaloids, was found to be an isomer of codeine and differed from it only in the position of the double bond. Hofmann degradation afforded β-codeimethine and neopine was, therefore, assigned the structure (XXII) [12].

Oripavine, the remaining member of this group was found to be the phenolic analogue of thebaine and was accordingly assigned the structure (XIXa) [13].

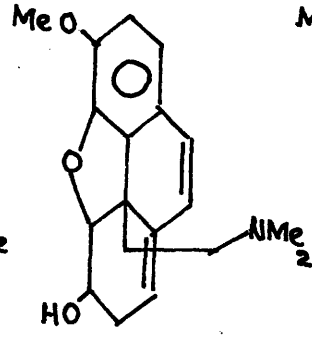


XIXa

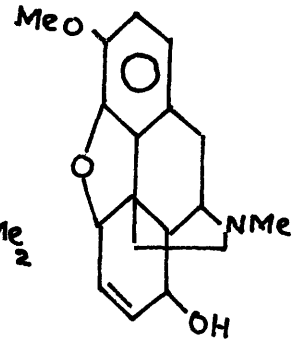
The Gulland-Robinson formulae could explain satisfactorily all the properties of morphine alkaloids. The α → β-codeimethine isomerisation can be formulated as (XXIII) → (XXIV). ε-Codeimethine (XXV), derived from ψ-codeine (XXVI), however, cannot achieve a similar increase in conjugation and consequently no isomerisation occurs.



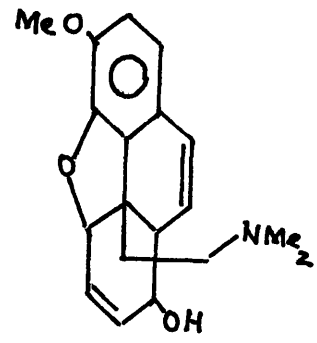
XXIII



XXIV

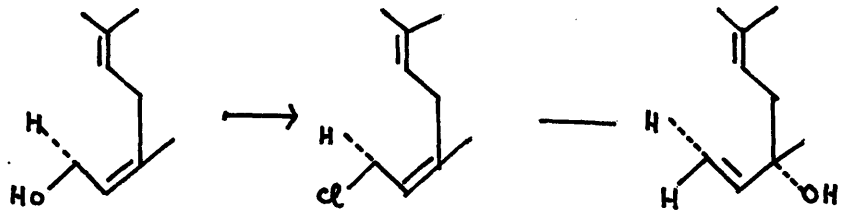


XXVI



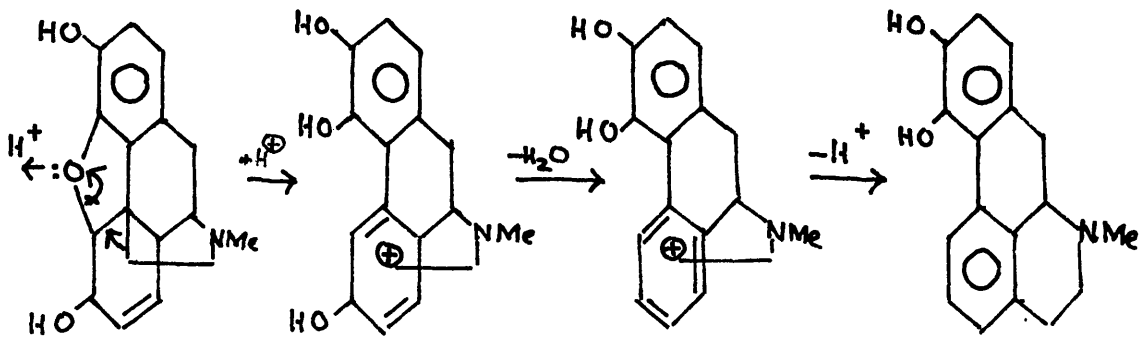
XXV

The transformation of codeine through halogenocodides to iso-, Ψ-, and allo- Ψ-codeine finds analogy in the conversion of geraniol (XXVl) to linaloöl (XXVll).

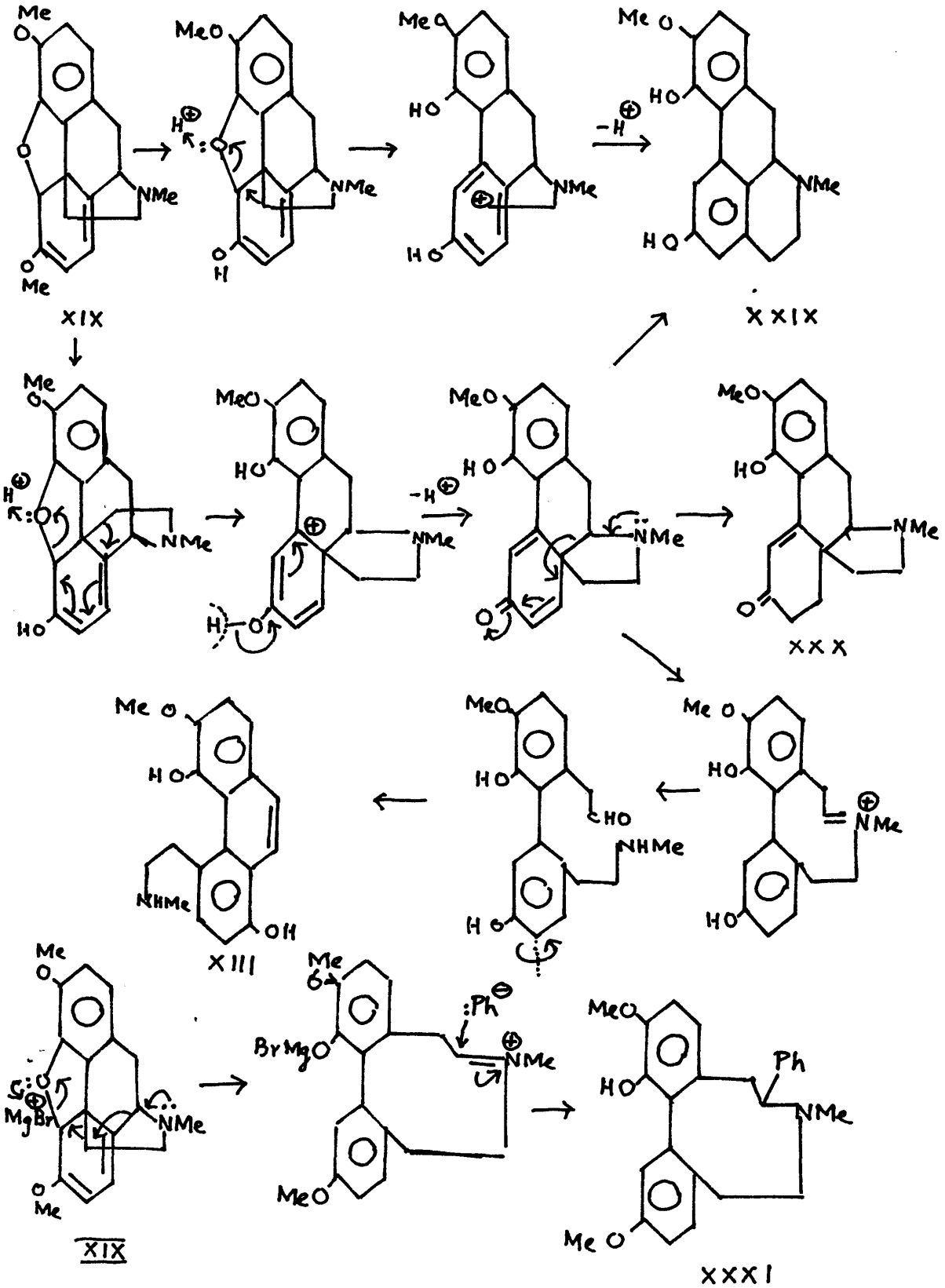


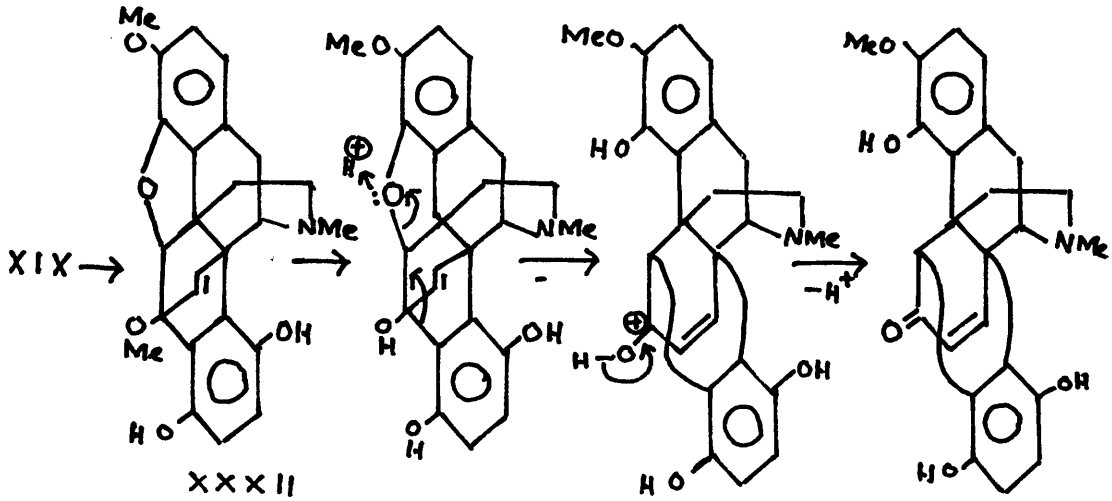
XXVI XXVII

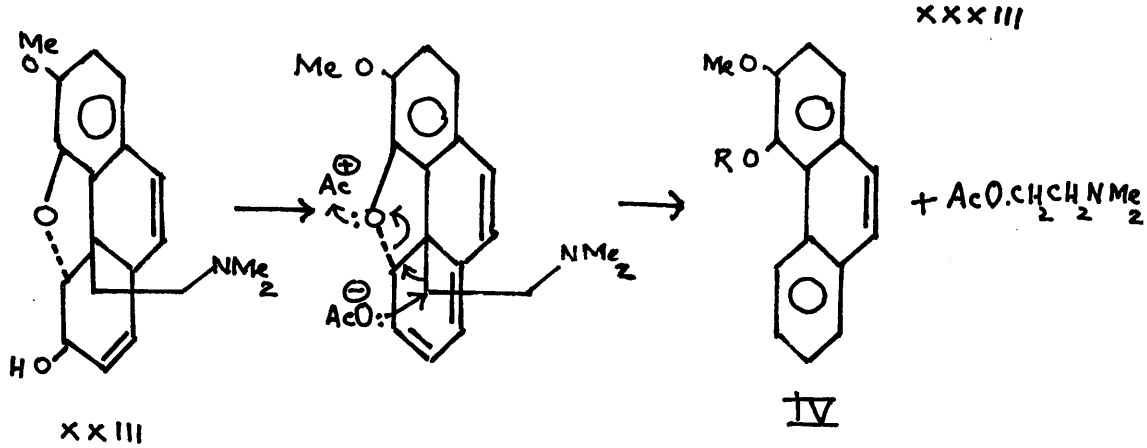
The various molecular rearrangements undergone by these alkaloids also find a satisfactory explanation in these formulae. Thus the transformations morphine (XXVlll) → apomorphine (X), thebaine (XIX) → morphothebaine (XXlX), thebaine (XIX) → thebenine (Xlll), thebaine (XIX) → metathebainone (XXX), thebaine (XIX) → phenyldihydrothebaine (XXXl), thebainehydroquinone (XXXll) → flavothebaone (XXXlll), α-codeimethine (XXlll) → acetylmethylmorphol (IV; R = Ac) and α-codeimethine (XXlll) → methylmorphenol (V; R = Me) can be explained satisfactorily as shown below:-

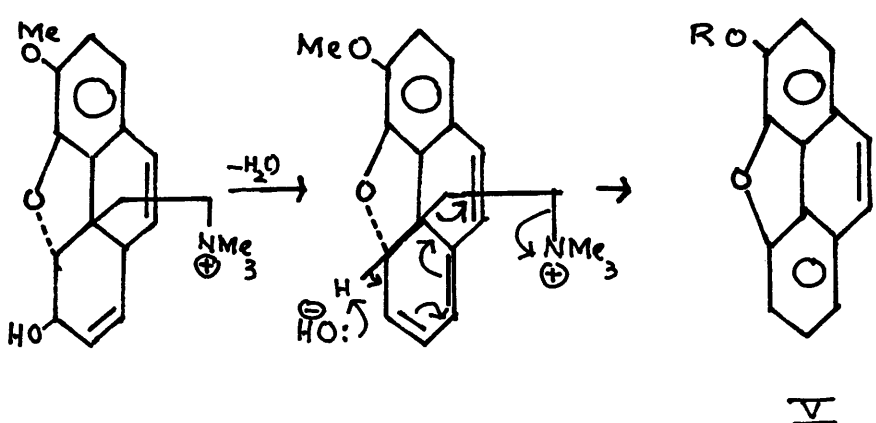


XXVIII X


Me
MeO
HO
NMe
NHMe
OH
MgBr
BrMgO
:Ph
Ph
XIX
XXIX
XXX
XIII
XXXI


XIX
XXXII
XXXIII

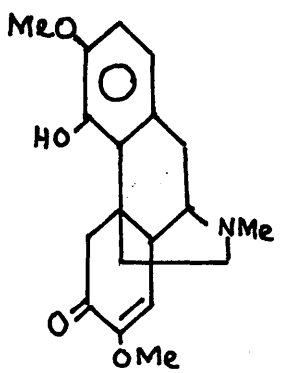

XXIII
IV
+ AcO.CH2CH2NMe2


-H2O
V

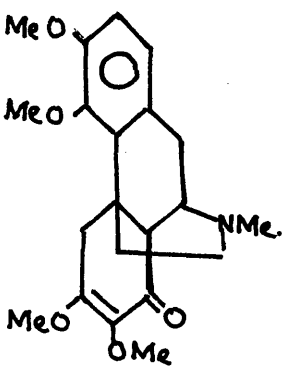
Finally, a complete confirmation of these formulae has been achieved recently by the synthesis of morphine by Gates and Tschudi [14] and of dihydrothebainone (and hence of morphine) by Ginsburg and his co-workers [15].

Following essentially similar methods of degradation, sinomenine, isolated from the Japanese plant Sinomenium acutum, has been assigned the structure (XXXIV) by Goto and his co-workers [16].

Hasubanonine, isolated from Stephanica japonica Miers, also showed close relationship to morphine alkaloids in its behaviour. It has been assigned the stfucture (XXXV) by Kondo and co-workers [17], [18]. It may be noted, however, that this formulation does not find an easy interpretation for its biogenesis in terms of oxidative phenol coupling mechanism.



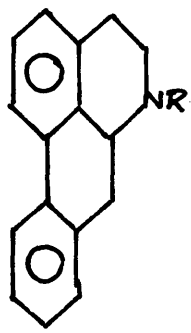
XXXIV



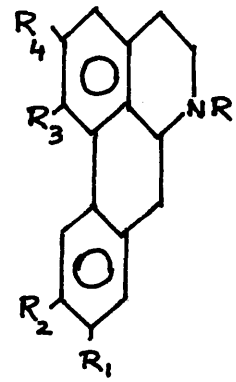
XXXV

The Aporphine Alkaloids.

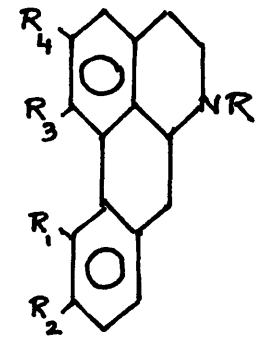
The aporphine alkaloids, represented by the basic structure (XXXVI), are widely distributed in Nature as tertiary bases (N-methyl) or secondary amines or quaternary salts. The biogenetic relationship between these alkaloids, and the benzylisoquinolines is fairly obvious and has been commented upon in detail at some other place. Apomorphine, and morphothebaine, the acid rearrangement products of morphine and thebaine respectively, also contain this basic skeleton, although they do not occur naturally, and have already been referred to.



XXXVI



XXXVII



XXXVIII

The majority of the naturally occurring aporphines contain four oxygen atoms and these belong mostly (exceptions crebanine and phanostenine) to either the Glaucine Type (XXXVII) or Corytuberine Type (XXXVIII). There are some, for example isothebaine, tuduranine, pukateine, anolobine, and possibly others which contain only three

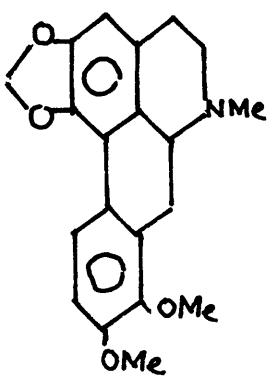
oxygen atoms whereas anonaine and roemerine have only two.

The chemistry of these bases has been elaborated by the usual methods applicable to other natural products and in particular to alkaloids and basic substances. While the synthetic evidence in support of the structures of natural products generally follows the accumulation of degradative data, the structures of a number of aporphines were established by synthesis long before a detailed degradation of the molecule was undertaken. The structure of glaucine (XXXVll; $R_1 = R_2 = R_3 = R_4 = R = Me$) was arrived at by Gadamer [19] by a process of intuitive reasoning supplemented by a synthesis. It was subjected to Hofmann degradation [20] much later and the results were found to be in agreement with the proposed structure. The usual sequence of reactions followed in the synthesis of aporphines is as follows:-

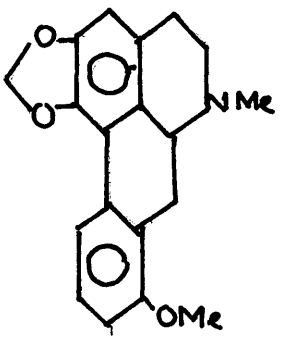
An appropriately substituted β-arylethylamine is reacted with a 6-nitrodialkoxyphenylacetic acid and the resultant amide cyclised according to the Bischler-Napieralski method. The resultant 1-(6-nitrobenzyl)-dihydroisoquinoline is then converted into its methiodide and then reduced whereby the nitro group is converted to an amine group and the hetero ring reduced to N-methyltetrahydro compound. The

N-methyltetrahydro compound is subsequently diazotised and cyclised by Pschorr's method of phenanthrene synthesis or a modification thereof to furnish the aporphine although the yield in the last cyclisation step is generally very poor [21].

The ultra violet spectra of aporphine bases [24] are characteristic and have been of great help in elucidating the structures of these bases. The aporphines, in general, i.e. those substituted in 2,3,4,5,6 positions exhibit two maxima (near 275 mμ and 300 mμ). Crebanine (XXXIX) carrying substituents at 1,2,5 and 6 position, however, shows only one maximum (at 280 mμ) with the second peak around 300 mμ virtually reduced to a shoulder [22]. Stephanine (XL) [23], likewise, shows a single maximum (at 270 mμ) and a broad shoulder at 292-320 mμ.



XXXIX



XL

Hofmann degradation has also been frequently helpful in the elucidation of the structures of aporphines. The first nitrogen free product in this case is an 8-vinylphenanthrene. The vinyl side chain is then oxidised to the carboxyl group and the resulting phenanthrene-8-carboxylic acid is either decarboxylated or the carboxy function converted into an alkoxy function in the usual way ($-CO_2H \rightarrow -CO_2NH_2 \rightarrow -NH_2 \rightarrow -OH \rightarrow -OR$) [29] and the resulting neutral phenanthrene derivative characterised and identified.

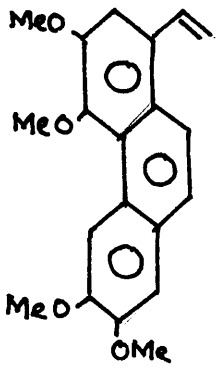
All these methods mentioned above are well illustrated in the case of laurifoline chloride, a phenolic quaternary base isolated recently from Cocculus laurifolius DC by Tomita and co-workers [25], as indicated below.

Preliminary examination in the usual way indicated the presence in laurifoline chloride, $C_{20}H_{24}O_4NCl$, of two methoxyl groups, two phenolic hydroxyl groups and one dimethylimino group so that the partial structure of laurifoline chloride could be written as:

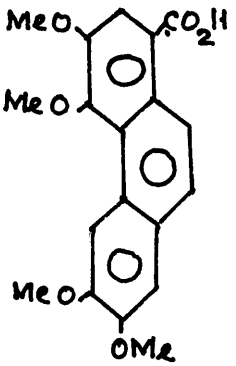
$$C_{16}H_{10} \begin{cases} (OMe)_2 \\ (OH)_2 \\ N^+(CH_3)_2Cl \end{cases}$$

A colour reaction indicated the possible existence of an aporphine skeleton and this received further support from its ultraviolet absorption spectrum which was fairly similar to that of the aporphine base, dicentrine. [$\lambda_{max.}^{H_2O}$ 279 mμ (log ε 4.05) and $\lambda_{max.}^{H_2O}$ 304 mμ (log ε 4.11)]. A two-stage Hofmann degradation of O,O-dimethyllaurifoline iodide afforded 2:3:5:6-tetramethoxy-8-vinyl phenanthrene (XLl) which was converted into 2:3:5:6-tetramethoxyphenanthrene (XLlll) via 2:3:5:6-tetramethoxy-8-carboxy-phenanthrene (XLll). A comparison of the data of the decomposition products (XLl) to (XLll) with those of the corresponding products of known aporphines suggested the identity of O,O-dimethyllaurifoline iodide with O,O-dimethylboldine methiodide (glaucine methiodide) and hence laurifoline chloride could be represented as (XLIV) [26]. The position of the two phenolic hydroxyl groups was decided by a study of similar Hofmann degradation of O,O-diethyllaurifoline iodide when the ultimate diethoxydimethoxy phenanthrene obtained was identified to be 2:5-diethoxy-3:6-dimethoxy phenanthrene and consequently laurifoline chloride was assigned the structure (XLV) [27]. Finally, this structure for laurifoline chloride was confirmed by its synthesis following the usual sequence of reactions starting with 3-benzyloxy-4-methoxy-6-nitrophenyl-N-(3'-

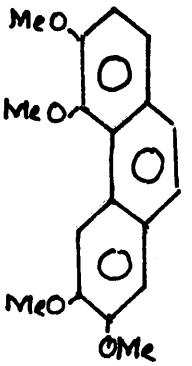
methoxy-4'-benzyloxyphenyl)ethylacetamide (XLVI) obtained from 3-methoxy-4-benzyloxyphenylethylamine and 3-benzyloxy-4-methoxy-6-nitrobenzoic acid in the usual way [28].



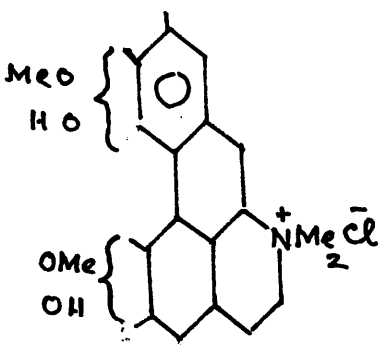
XLI



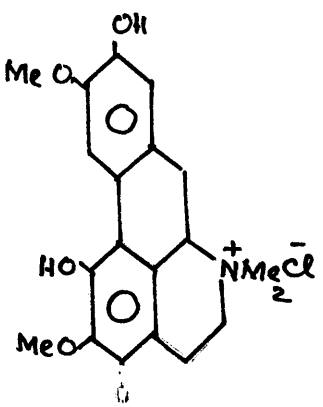
XLII



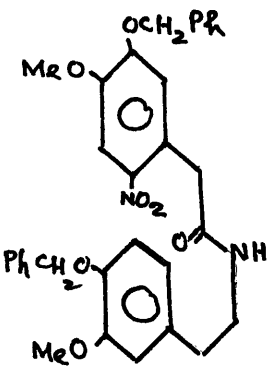
XLIII



XLIV



XLV



XLVI

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18. Cf. Bentley, Experientia, 1956, 12, 251.

19. Gadamer, Arch. Pharm., 1911, 249, 680.

20. Warnat, Ber., 1926, 59, 85.

s.a. Warnat, Ber., 1925, 58, 2768.

21. See, for example,

a) Hey and Lobo, J., 1954, 2246.

b) Tomita and Kikkawa, J. Pharm. Soc. Japan, 1957, 77, 195.

22. Govindachari, Nagarajan and Ramadas, J., 1958, 983.

23. Tomita and Hirai, J. Pharm. Soc. Japan, 1957, 77, 290.

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26. idem., ibid., 1953, 1, 5.

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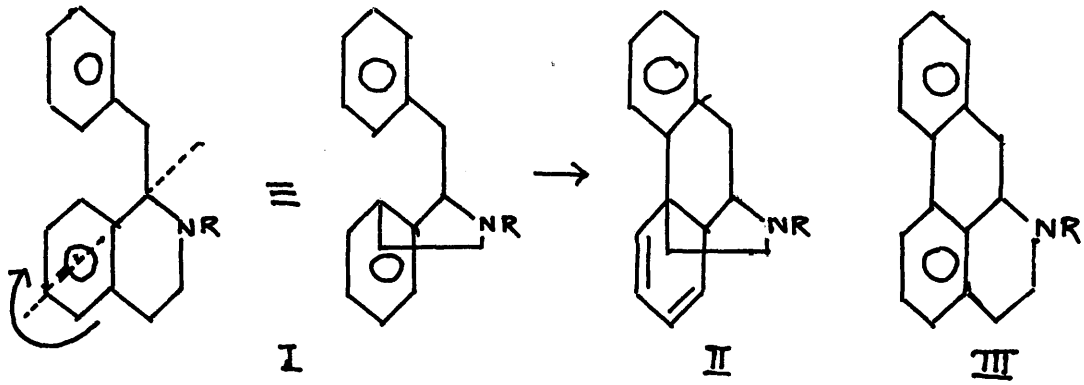
SECTION II

[References in this Section appear on page 212]

BIOGENESIS OF MORPHINE ALKALOIDS - HISTORICAL

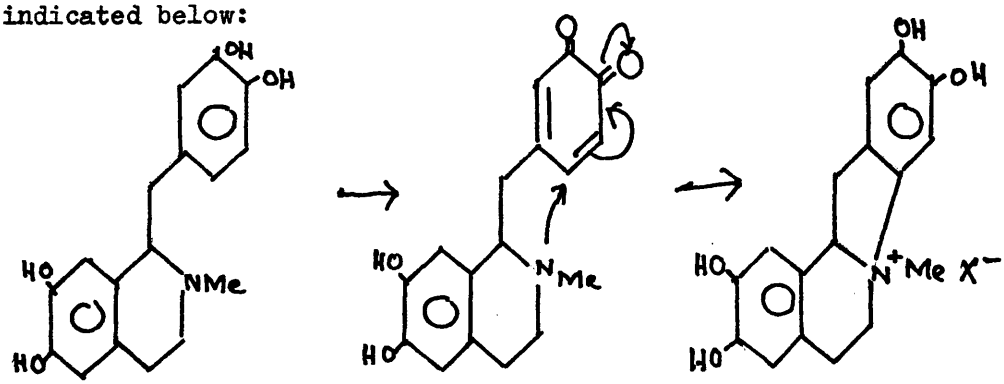
The processes by which morphine alkaloids are built up in Nature have long been the subject of study and speculation among organic chemists and the desire to unravel this mystery has received a particular stimulus by the recent publication of the total synthesis of morphine [1], the first vegetable alkaloid to be discovered.

It was appreciated fairly early in the otherwise long chapter of 'morphine chemistry' that the probable mode of biogenesis of morphine alkaloids involves the union of two aromatic nuclei of a laudanosine type benzyltetrahydroisoquinoline [2]. This proposal was apparently motivated more by the desire to equate the structures of the morphine-thebaine group of alkaloids with those of other opium bases, and the mechanism of this biogenetic route does not appear to have been much appreciated at that time. Thus the lower ring of the laudanosine skeleton (I), as usually written, was supposed to be twisted about the axis and in the direction shown and this was followed by 'ring closure' in some way leading to the blocked hydroaromatic system (II) of morphine alkaloids.



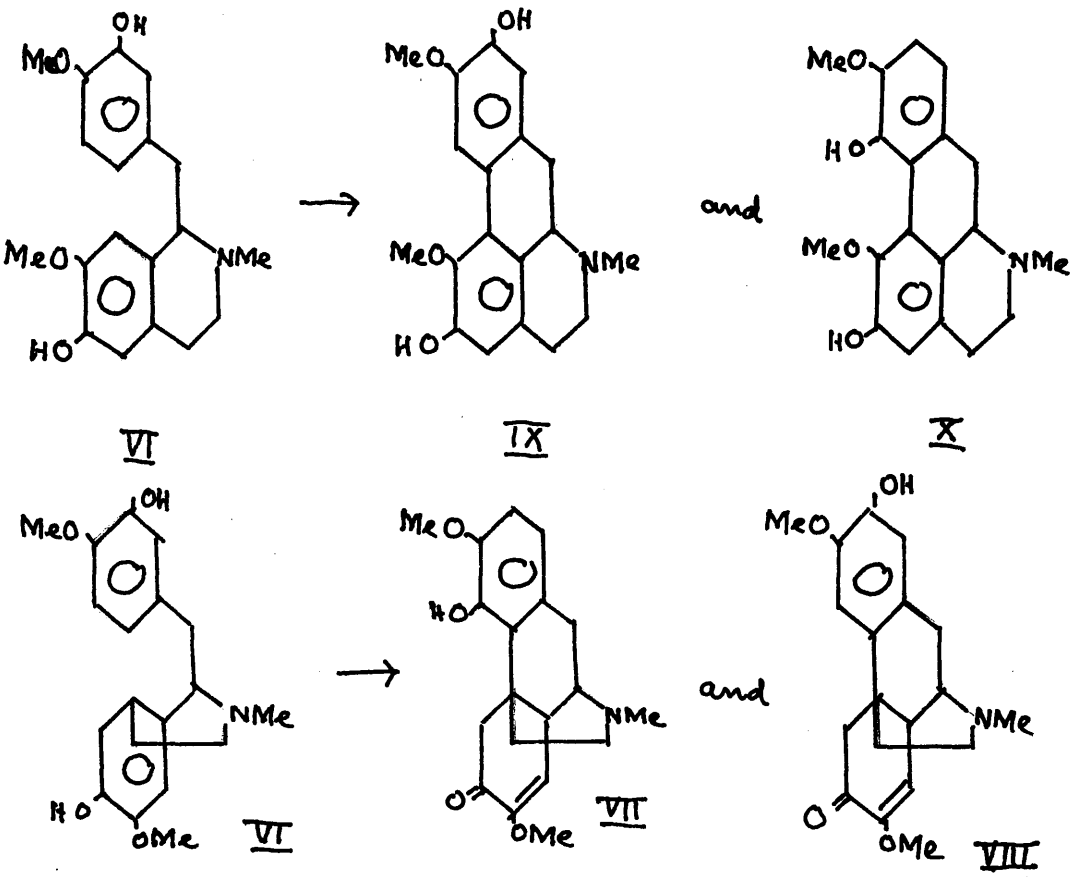
I II III

It was, of course, appreciated at the same time that the skeleton of aporphines (III) also could arise from the laudanosine type skeleton (I). Attempts were also made to simulate this process by oxidising laudanosoline (IV) under mild conditions [3], [4], [5], but in each case only 2:3:11:12-tetrahydro-8-methyldibenzotetrahydropyrro colinium chloride (V) was obtained rather than the anticipated aporphine type base. The formation of (V), probably, follows the mechanism indicated below:



IV IV A V

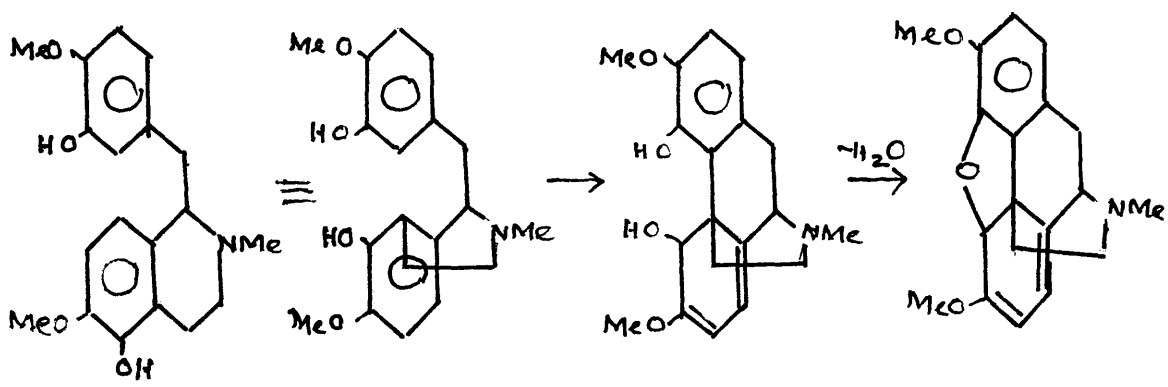
Laudanosoline-4':7-dimethyl ether (VI) was accordingly considered as 'protosinomenine' [2], [6] from which the alkaloid sinomenine (VII) and an isomeric sinomenine (VIII), hitherto unknown in Nature, besides the aporphine bases (IX) and (X) corresponding to glaucine and corytuberine type respectively would be supposed to have been built up.



While this so-called 'protosinomenine' (VI) was never obtained in amounts sufficient to test the validity of the above

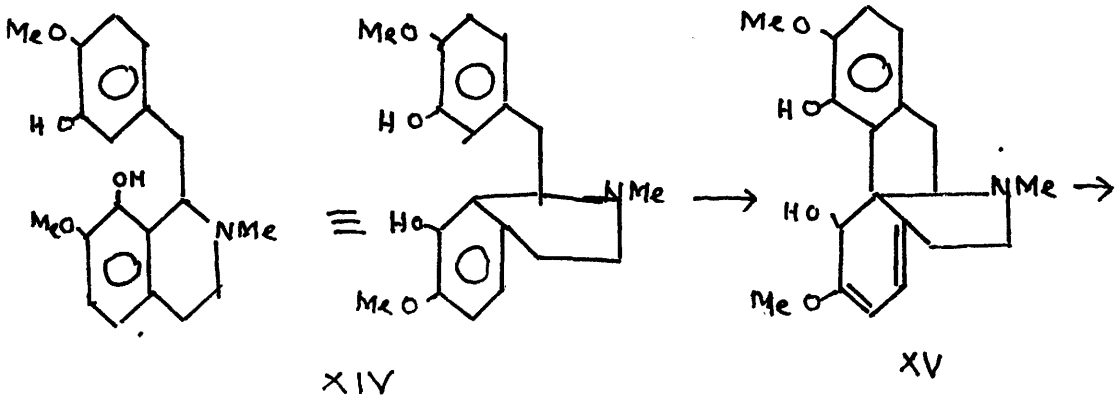
hypothesis, the postulated formation of (VII), and also of (VIII), (IX) and (X) from (VI), in any case, is not easy to understand and appears incompatible with the theory of oxidative coupling of phenols [7] which require the presence of hydroxyl groups in positions ortho or para to the points of ring closure.

It was observed at the same time by Robinson and Sugasawa [2] that while the orientation of oxygen substituents in the benzene rings of 'protosinomenine' (VI) is identical in the two halves of the molecule and corresponds to that in 3:4-dihydroxyphenylalanine (DOPA), that in the possible isoquinoline precursor (XI) for the biogenesis of thebaine (XIII), as shown below (XI) → (XIII), lacks this arrangement and the formation of (XI) would require the union of two dissimilar fragments, namely 3:4-dihydroxyphenylacetaldehyde and β-(2:3-dihydroxy phenyl)ethylamine derivable from the corresponding phenylalanines.

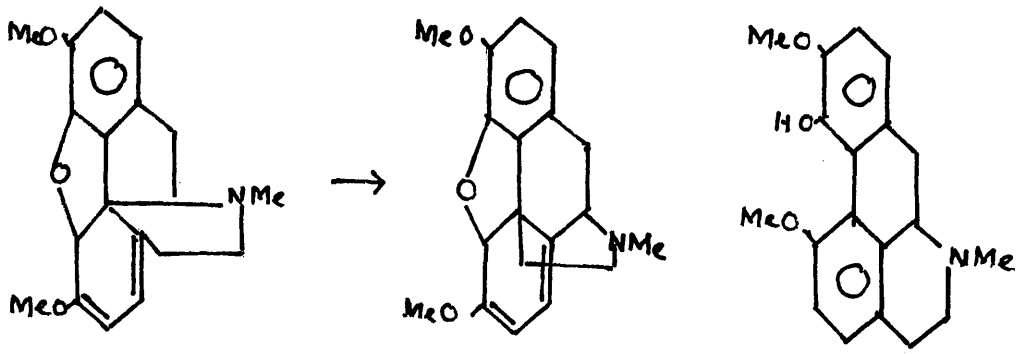


XI XII XIII

However, the fact that such an arrangement of oxygen substituents as in (XI) was unknown in Nature, prompted Robinson and Sugasawa to postulate (XIV) as 'protothebaine'. This 'protothebaine' (XIV) could arise from the same intermediates as (VI) with the cyclisation of the isoquinoline ring ortho instead of para to the hydroxyl group. Thebaine (XIII) would then arise from (XIV) according to the scheme outlined below. This involves the oxidative cyclisation of (XIV) to (XV) followed by formation of the 4:5-oxide bridge through the dehydration of (XV) to (XVI). (XVI) would then probably suffer transposition of substituents at C-13 and C-14 furnishing thebaine (XIII). The isolation of isothebaine (XVII) [8], [9] instead of thebaine from the roots of Papaver orientale during the period of withering and the rest of the plant was taken as evidence in support of this hypothesis, it being suggested that isothebaine was formed from (XIV) by elimination of elements of water [10].



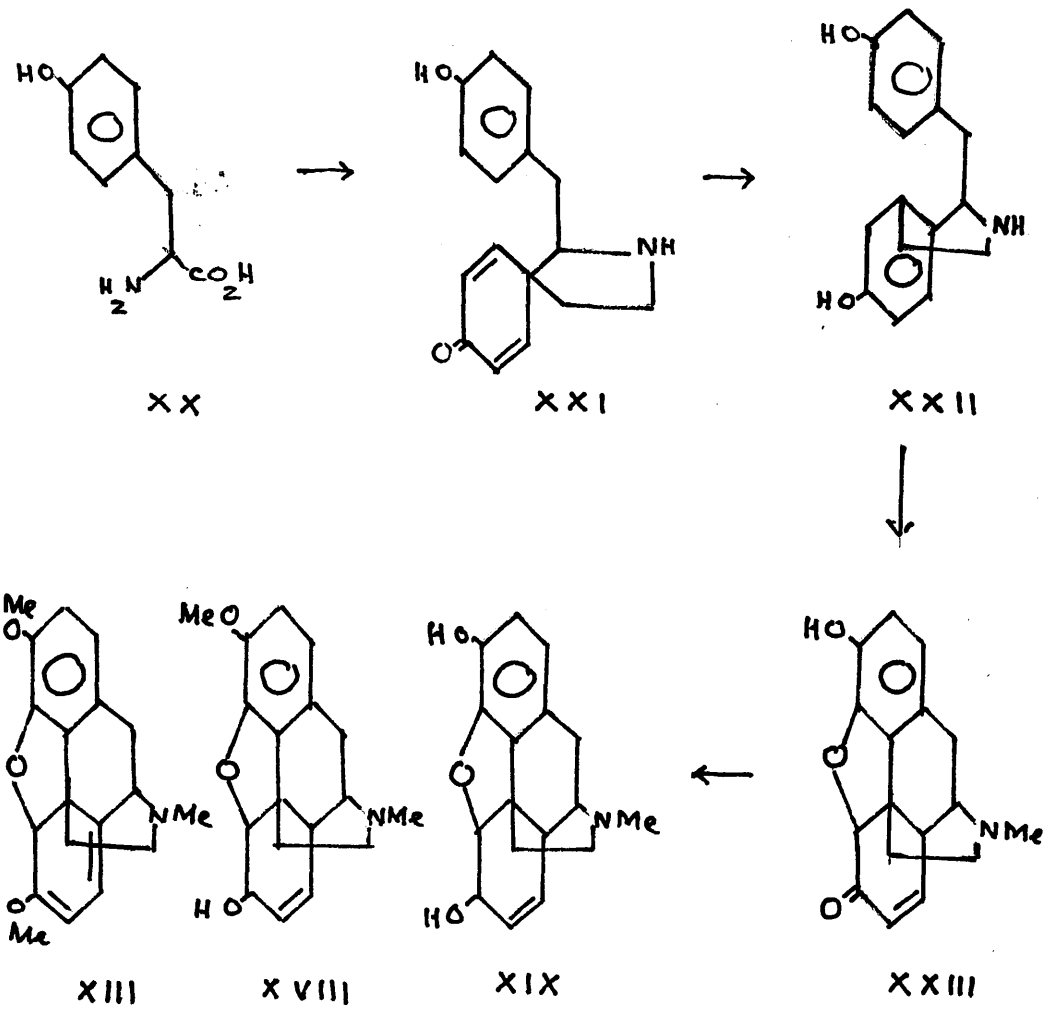
XIV XV



XVI XIII XVII

It will be noticed that this latter scheme, as does the scheme [(XI)→ (XII) →(XIII)], involves the formation of the 4:5-oxide bridge through a mechanistically improbable mode of dehydration [see (XV)→ (XVI)]. In addition, the transformation of (XVI) to (XVII) is not very easy to visualise.

More recently, Robinson [11], [12] has suggested a somewhat modified scheme for the biogenesis of thebaine (XIII) and hence of codeine (XVIII) and morphine (XIX). Here again, Robinson has attached great importance to the apparent lack of DOPA (3:4-dihydroxyphenylalanine) orientation of oxygen atoms in thebaine. He, therefore, starts with tyrosine (XX). (XXI) is postulated as the first intermediate which would suffer molecular migration to furnish the intermediate (XXII) and this would then be transformed, through unspecified stages, into morphinone (XXIII) thereby affording morphine (XIX), codeine (XVIII) and thebaine (XIII).

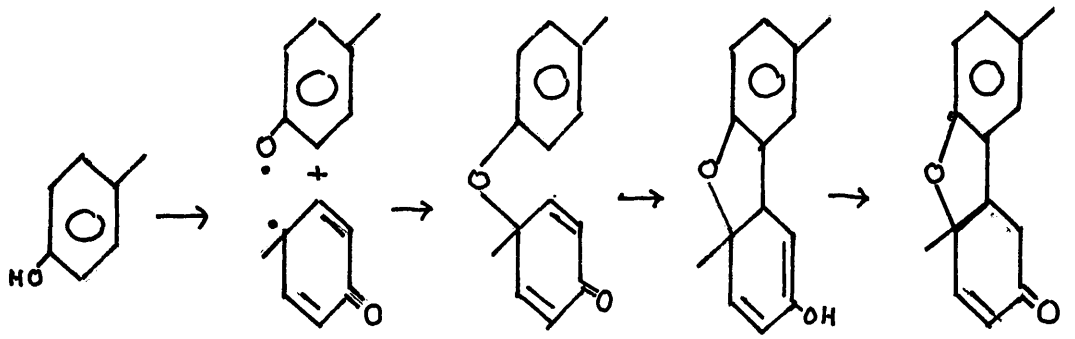


XX XXI XXII XXIII XIX XVIII XIII

The author has refrained from discussing biogenetic details and this in itself is a serious criticism of this scheme which involves so many highly speculative stages.

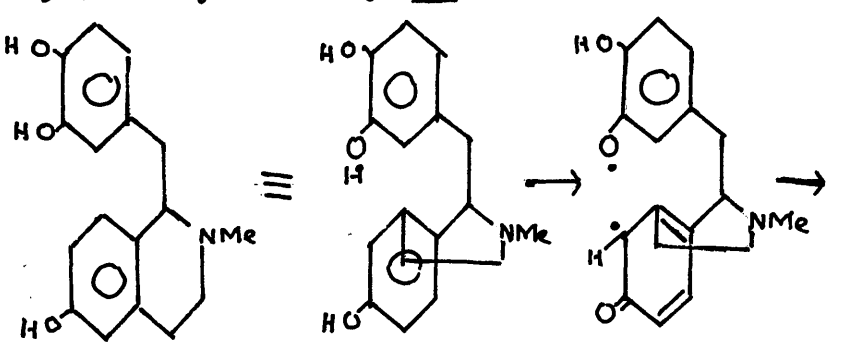
A new approach to the problem of the biogenesis of morphine alkaloids was made by Schöpf [13]. His choice of (XXIV) as the suitable precursor in the biogenesis of morphine alkaloids was based

by analogy with the oxidation product of p-cresol, formulated by Pummerer and his co-workers [14], [15] as (XXV). This ketonic dimer from p-cresol (XXVI) had a dibenzofuran ring, an aromatic nucleus, a quaternary carbon atom and a reduced ring containing a double bond and an oxygen substituent. All these characters are common to morphine alkaloids except sinomenine and hasubanonine. He believed that Pummerer's ketone (XXV) is formed by the mechanism outlined below:

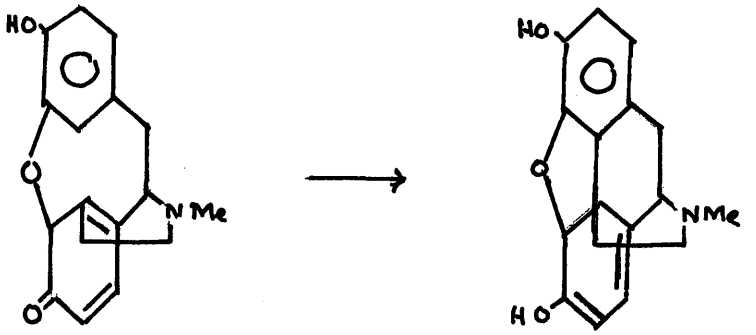


XXVI XXV

Following a similar line of argument, he considered the precursor (XXIV) to arise from 1-(3':4'-dihydroxybenzyl)-6-hydroxy-1:2:3:4-tetrahydro-2-methyl-isoquinoline (XXVII) as shown below:

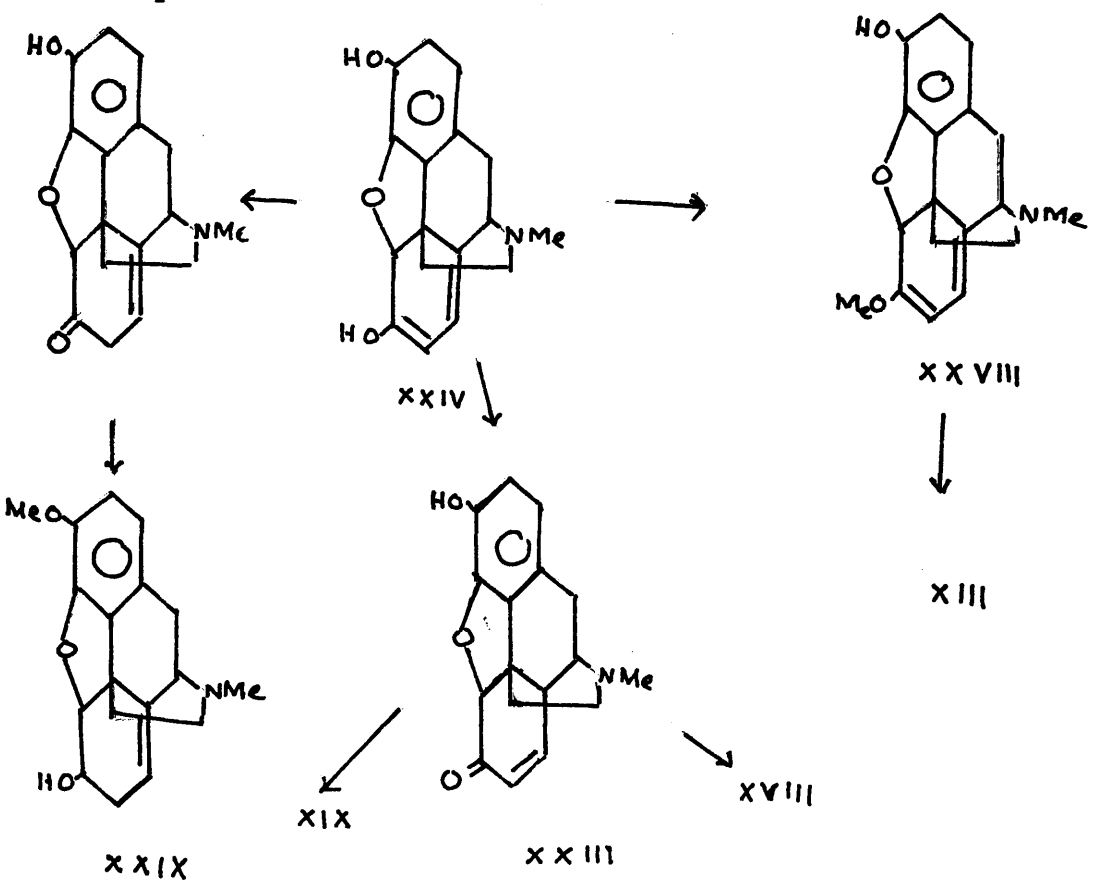


XXVII



XXIV

The key substance (XXIV) could then give rise to the various morphine alkaloids as shown below:



XXIV

XXVIII

XIII

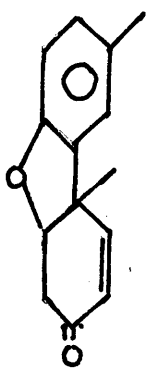
XIX

XXIII

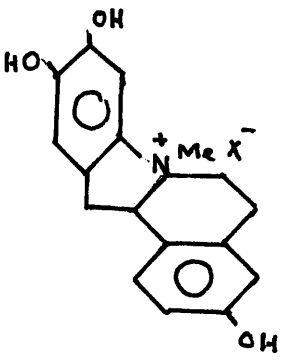
XVIII

XXIX

But as already pointed out in Chapter I, Barton et al. [7] established decisively the erroneous formulation of Pummerer's ketone as (XXV) and consequently the whole basis of Schopf's hypothesis regarding the biogenesis of morphine alkaloids was shaken. In any event, all attempts to convert (XXVll) or suitable derivatives led to the production of only pyrrocolinuim salts (XXX) like the one already encountered in the case of oxidation of laudanosoline.

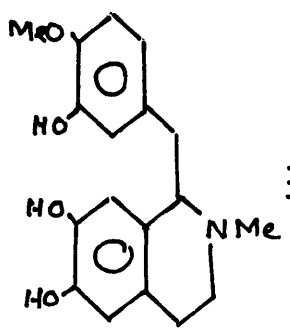


XXVa

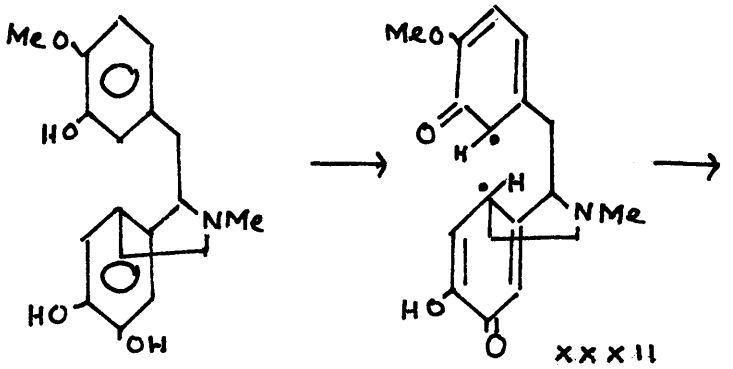


XXX

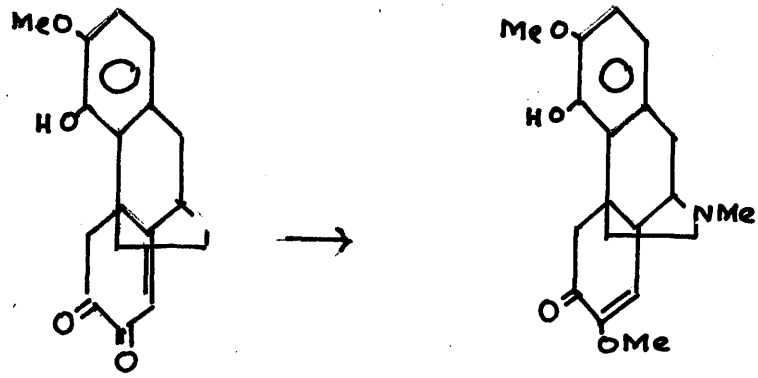
Schöpf had at the same time proposed laudanosoline-4'-methyl ether (XXXl) as 'protosinomenine' and suggested the following scheme for the biogenesis of sinomenine (Vll):-



XXXI



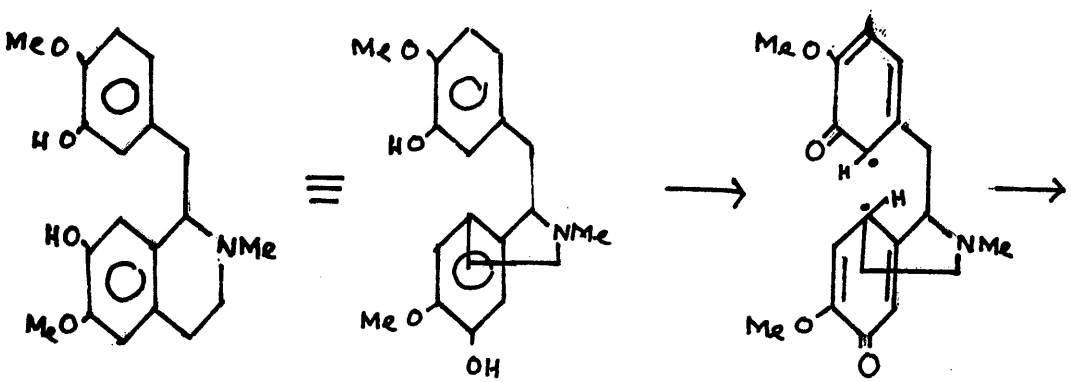
XXXII



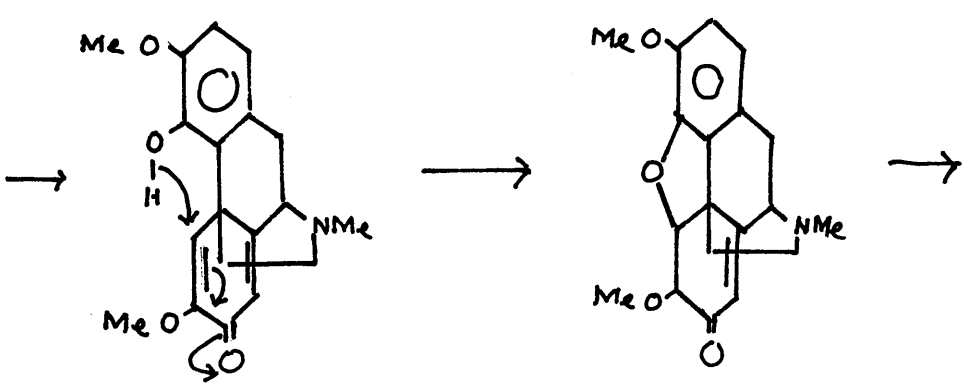
XXXIII XVII

The revised structure (XXVa) for the neutral, ketonic dimer obtained by the oxidation of p-cresol and the inherent theoretical implications of that work led Barton and Cohen [16] to put forward an alternative biogenetic scheme for the morphine alkaloids in which laudanosoline-4':6-dimethyl ether (XXXIV) is postulated not only as 'prototheba*i*ne' (and hence the precursor for most of the remaining morphine alkaloids, namely codeine, morphine etc.) but also as 'protosinomenine'. It will be noticed that (XXXIV) can be formed from the two fragments having the DOPA orientation of oxygen atoms -

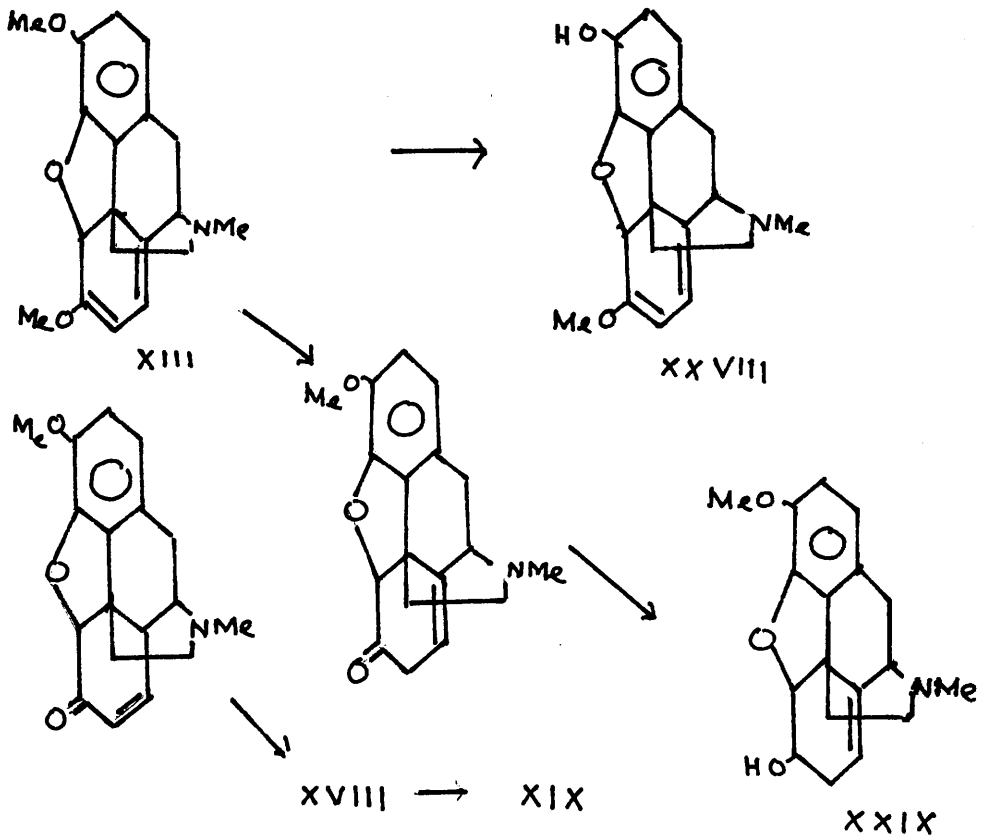
the apparent lack of which in thebaine, morphine and codeine was emphasised so much by Robinson (loc. cit.). Moreover, this scheme does not suffer from the theoretical difficulties already referred to in connection with the earlier views about the biogenesis of morphine alkaloids. All the important morphine alkaloids, namely morphine (XIX), codeine (XVIII), thebaine (XIII), oripavine (XXVIII), neopine (XXIX) can be derived from the postulated precursor (XXXIV) as illustrated below:-



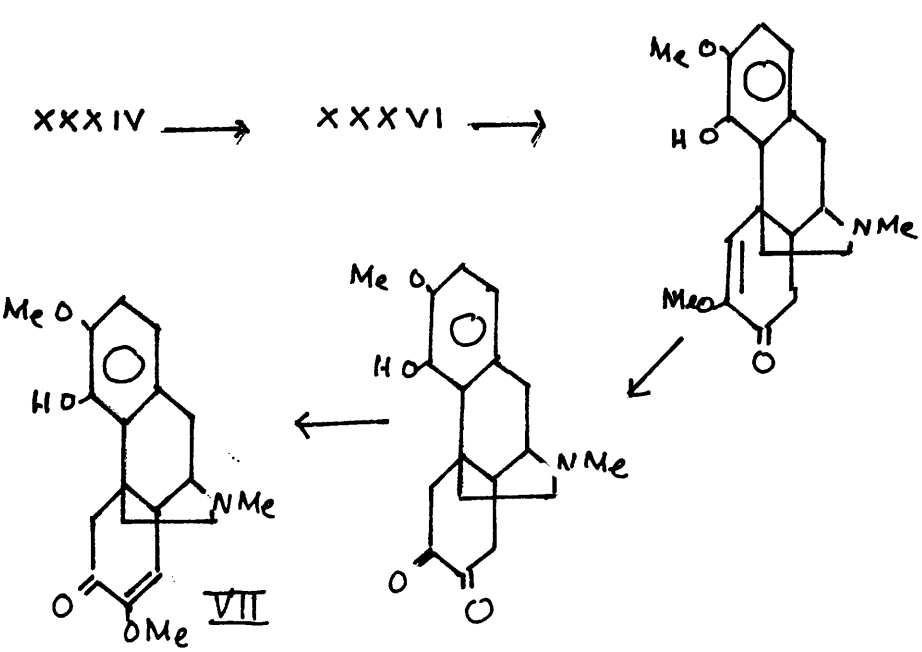
XXXIV XXXV



XXXVI XXXVII

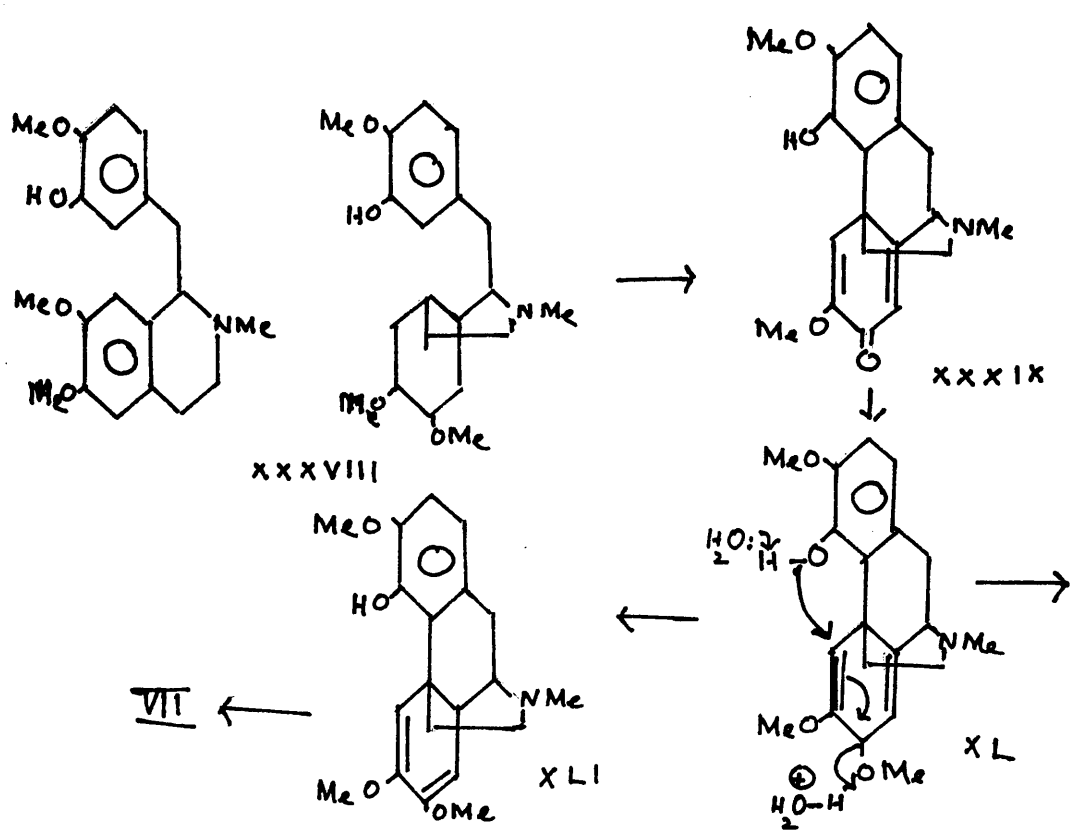


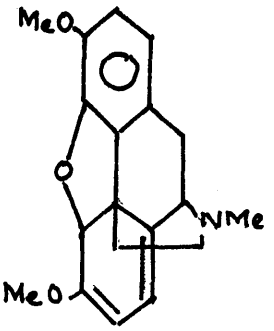
The genesis of sinomenine (VII) from (XXXIV) can be illustrated as follows:-



It has been the object of the present work to see if one could develop 'in vitro' conditions for the conversion of laudanosoline-4':6-dimethyl ether (XXXIV) into some morphine and/or aporphine alkaloids.

Bentley [17] has more recently suggested a possibility that thebaine (XIII) and hence other morphine alkaloids and sinomenine (VII) can arise from laudanine (XXXVIII) through a radical substitution reaction. An intramolecular radical substitution would afford (XL) which would suffer ring closure of the 4,5-oxide bridge by the allylic expulsion of a methoxyl group as shown:-



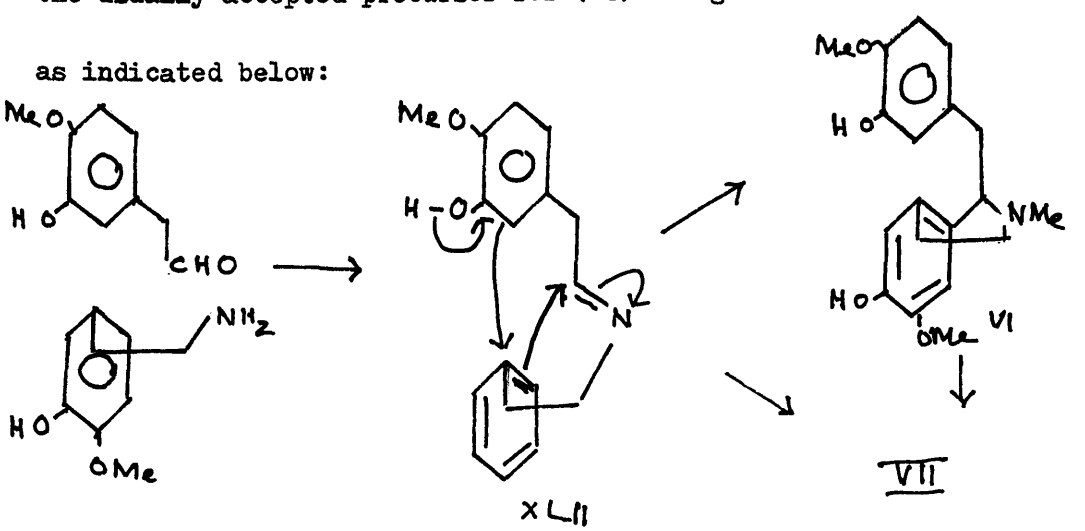


XIII

XIX

XVIII

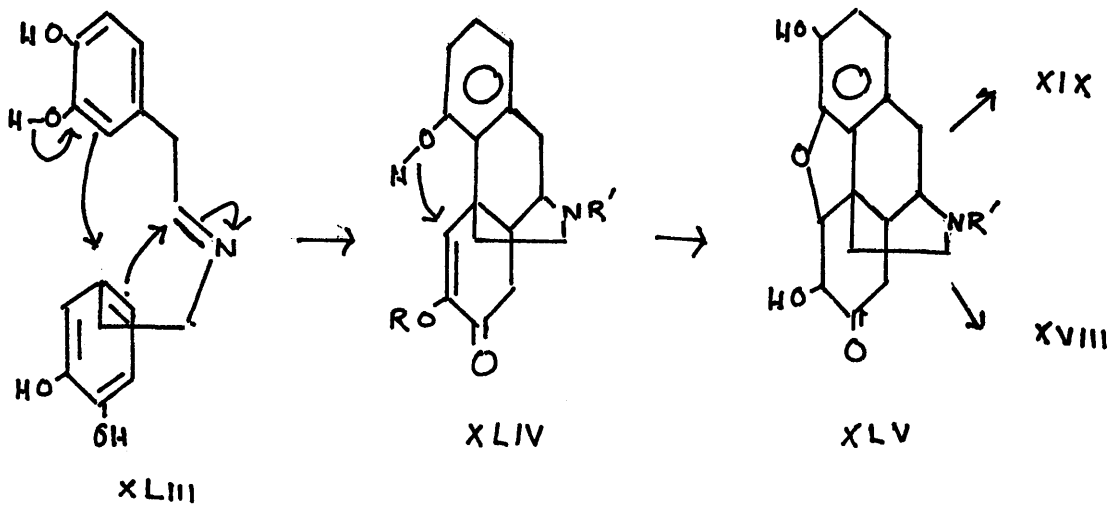
Cohen [18] has advanced still another view for the biogenesis of some morphine alkaloids. This view, though not involving oxidative phenol coupling, gives a reasonable route for the genesis of sinomenine (VII), morphine (XIX) and codeine (XVIII). Thus he rationalises the formation of sinomenine (VII) from Robinson's 'protosinomenine' (VI) through an alternative mechanism. (XLII), the usually accepted precursor for (VI) can give rise to sinomenine as indicated below:



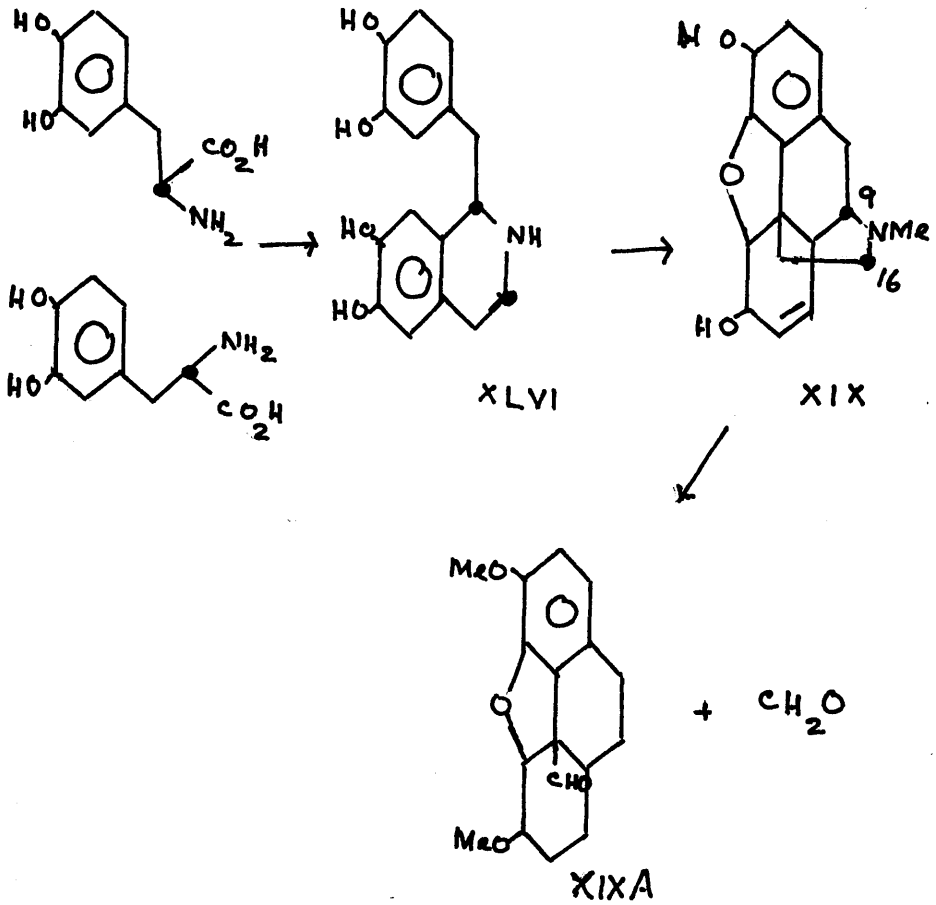
XLII

VII

The formation of morphine (XIX) and codeine (XVIII) has also been indicated in this scheme as shown below:



Battersby and Harper [19] have recently adumbrated the biosynthesis of all the major alkaloids of the morphine group by feeding the plant Papaver somniferum using labelled α-^{14}C-DL-tyrosine. The recovered morphine (XIX) was converted into codeine methyl ether and this was degraded in the usual way, to yield formaldehyde, isolated as the dimedone derivative, and the aldehyde (XIXA), isolated as the oxime. Activity measurements of these degradation products showed that half the activity of the original morphine is located at position 16 and thereby established that tyrosine is an efficient precursor of morphine.



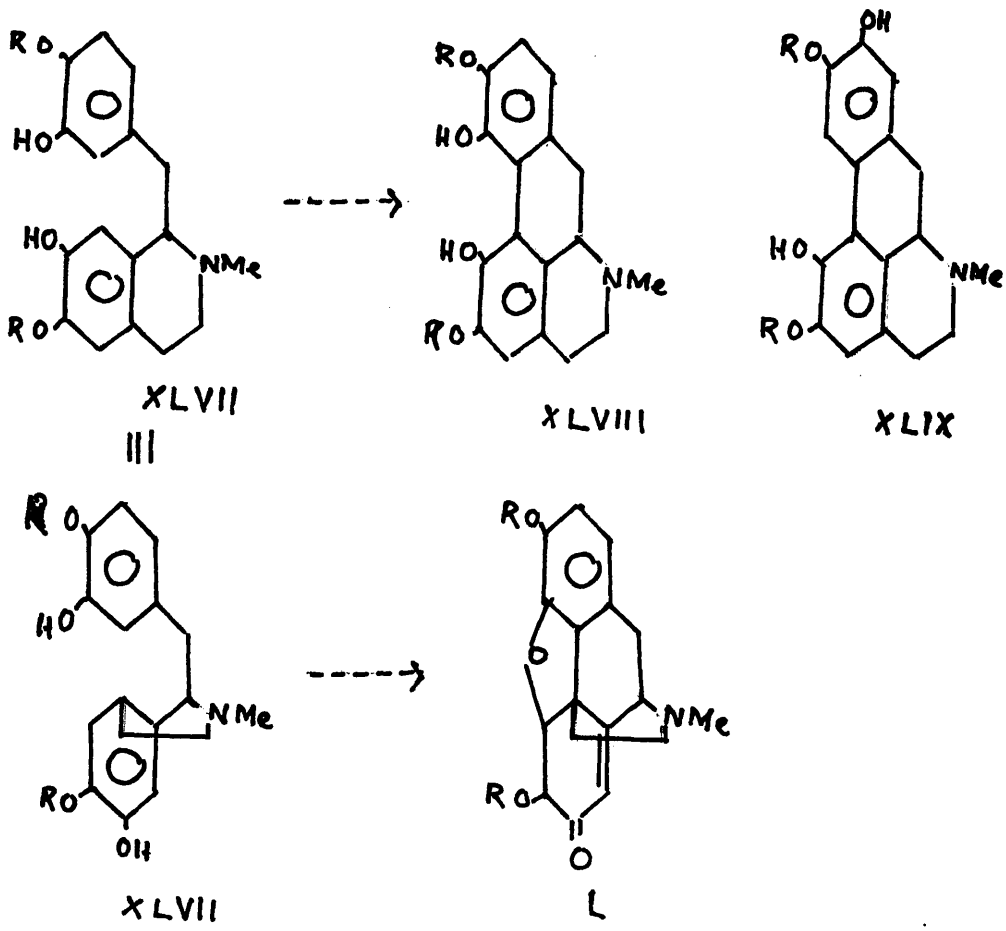
[The thick dots in the above formulae indicate the pattern of labelling].

Independent experiments of Leete [20] along similar lines have confirmed these results. Comparative studies on the feeding of the plant with α-^{14}C-DL-phenylalanine and α-^{14}C-DL-tyrosine indicated that tyrosine was incorporated to a greater extent suggesting thereby

probable hydroxylation of phenylalanine before transformation into morphine. While these experiments seem to support the postulated structural relationship of the benzylisoquinoline alkaloids, having the skeleton (XLVI), and hence of morphine alkaloids, to dihydroxy phenylalanine, they do not of course give precise information about the mechanism by which the transformation of (XLVI) into morphine (XIX) is brought about.

As mentioned above, the purpose of this investigation has been to see if we could develop 'in vitro' conditions for the conversion of laudanosoline-4':6-dialkyl ether into the alkaloids of aporphine and/or morphine type.

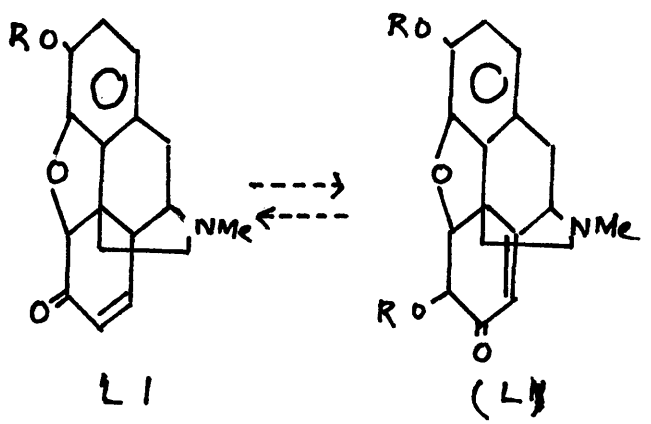
The immediate need for achieving this objective was to prepare the phenolic precursor, laudanosoline-4':6-dialkyl ether (XLVII) in quantity which we would then attempt to couple by oxidation hoping to get the aporphines (XLVIII) and/or (XLIX) and/or the morphine type compound (L).



It was appreciated at the same time that the above coupled products (XLVIII), (XLIX) and (L), if formed, would not result in any high yield. Moreover, the oxidation products would have the usual complexity associated with phenol oxidations as already explained in Chapter I.

The anticipated low yield of (L), if obtained, necessitated a particular care in the handling of the oxidation reaction as this

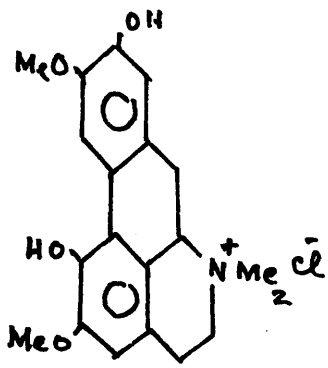
product (L) has to go through a number of exploratory stages before it would be converted into some known morphine type compound for comparison etc.. It was, therefore, considered desirable to prepare some 'model compounds', readily and reversibly obtainable from morphine, on which the preliminary experiments for conversion into (L) and vice versa could be carried out. Of course, the coupled product (L) itself should be easily identified from the oxidation mixtures by virtue of its characteristic spectroscopic behaviour as distinguished from that of the starting phenol (XLVll) or other possible oxidation products. The morphinone (LI) was accordingly chosen as the 'model compound' for this purpose.



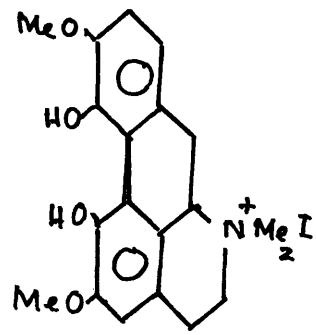
LI (L)

The aporphine type bases (XLVlll) and (XLIX), if formed, should not be difficult to identify provided suitable conditions for the oxidation of (XLVll) were established and a reasonable enrichment

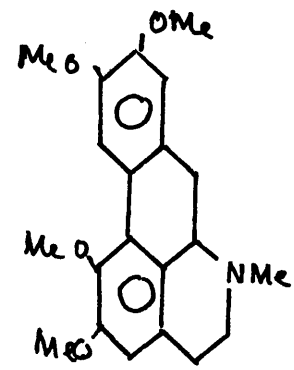
of these in the oxidation mixture accomplished. Some of the aporphines corresponding to these two types are already known to occur in Nature and some of their derivatives are also well characterised compounds. Thus laurifoline (LII) [21], magnoflorine (LIII) [22], [23], [24], corytuberine (XLVIII; R = Me) and glaucine (LIV) are all well known natural aporphine alkaloids. Corytuberine dimethyl ether is also a fairly well-characterised compound.



LII



LIII



LIV

It is also significant to note that another alkaloid coclanoline, isolated from Cocculus laurifolius DC. along with the quaternary aporphines laurifoline and magnoflorine [21] has recently been shown to have the structure (XLVII; R = Me). While we have independently synthesised laudanosoline-4':6-dimethyl ether

(≡coclanoline), syntheses of laurifoline [21], magnoflorine [22] and coclanoline [21], [22] have been reported. In any case, the occurrence of these bases together in the same plant is significant from the biogenetic point of view and lends further support to the hypothesis on which the present work was based.

The identification of aporphines (XLVIII) and (XLIX) is further facilitated by their characteristic ultra violet spectra. Thus while the parent phenol (XLVII) has only a single maximum at about 280 mμ with a sharp drop in intensity of absorption after 290 mμ, the coupled products (XLVIII) and (XLIX) would exhibit two maxima, one at about 275 mμ and the other near 300 mμ.

So from all this it appeared that the identification of (XLVIII), (XLIX) and (L), if formed, in the oxidation mixture obtained by oxidation of laudanosoline-4':6-dialkyl ether (XLVII) would be feasible, provided we are able to develop conditions suitable to induce a specific coupling furnishing a reasonable yield of these desired products. Of course, the difficulties that were likely to be faced in this task of orienting molecules in Nature's way with the crude laboratory methods, were not underestimated, but the developed modern techniques of organic chemistry gave some encouragement to undertake this rather bold aim of imitating Nature.

In view of the considerable amount of work that still lay ahead of us even when this laudanosoline-4':6-dialkyl ether (XLVII) had been obtained in sufficient amounts, it was natural to prefer a short and simple route to its synthesis, if possible. We were encouraged in this aim by a reported selective demethylation of laudanosine (LX, see Flowsheet II, page 141A) to laudanosoline-3':7-dimethyl ether (LXI) with anhydrous aluminium chloride in a 50% yield [25]. This latter laudanosoline-ether (LXI) appeared a promising intermediate for the projected synthesis of laudanosoline-4':6-dialkyl ether (XLVII) if the phenolic hydroxyl groups present in (LXI) could be converted into ether groups which would remain unaffected when the methoxyl groups already present are removed subsequently. Analogies for such selective demethylations are already known in the literature. Guaiacol isopropyl ether was cleaved to o-isopropoxyphenol by sodium in liquid ammonia [26]. Also, preliminary experiments on model compounds, namely nerolin (β-naphthol methyl ether), β-naphthol-isopropyl ether, and guaiacol isopropyl ether gave results which indicated that alkaline hydrolysis with 5% potassium hydroxide in diethylene glycol at 180° for two hours of guaiacol isopropyl ether led to the selective hydrolysis of methoxy groups while the isopropoxy groups remained unaffected. It was, therefore, decided to prepare

the diisopropyl ether of laudanosoline-3':7-dimethyl ether (LXl) and subject the resulting non-phenolic base (LXll; R = i-Pr) to selective demethylation with the hope of securing the desired phenolic precursor, laudanosoline-4':6-diisopropyl ether (LXlll; R = i-Pr).

Synthesis of laudanosoline-4':6-diisopropyl ether (LXlll; R = i-Pr).

(See Flowsheet II, page 141A).

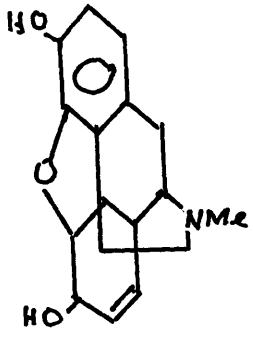
Laudanosine (LX) was prepared from papaverine (LVlll) through papaverine methiodide (LIX) essentially according to Awe and Unger's method [27] in a yield of only 40-45% although these workers have recorded an almost quantitative yield. Demethylation of laudanosine with twice sublimed aluminium chloride (fresh) in twice distilled nitrobenzene under the conditions used by Schöpf and Thierfelder [25] afforded, in our hands, only a product of variable quality and that in very poor yield. The product was isolated as the hydrobromide whose separation was extremely slow. Moreover, the hydrobromide thus obtained melted over a very wide range and there was no improvement in the melting point even after repeated recrystallisations although the yield dropped considerably after each recrystallisation. This was presumably due to the difficulty of arresting demethylation at a particular stage and the product resulting from the demethylation of

laudanosine is most probably a very complex mixture of different possible isomers of laudanosoline-ethers. All attempts using purest reagents and widely varying reaction conditions, however, led to similar results without any improvement in the yield or quality of the product. The product, supposedly laudanosoline-3':7-dimethyl ether, was then isopropylated using isopropyl iodide in methanolic potassium hydroxide under an atmosphere of nitrogen, in the usual way. The resulting oil, however, could not be induced to crystallise but a very small yield of a styphnate was obtained from this oil and this styphnate analysed correctly for laudanosoline-3':7-dimethyl-4':6-diisopropyl ether styphnate. In later experiments intended for improving the yield of this styphnate if possible, even the small yield of this crystalline styphnate disappeared and all further experiments to repeat the isopropylation of laudanosoline-3':7-dimethyl ether were unsuccessful, only intractable brown tars being obtained. Demethylation of the small amount of the supposed (LXll; R = i-Pr) prepared above by sodium in liquid ammonia, however, led to inconclusive results.

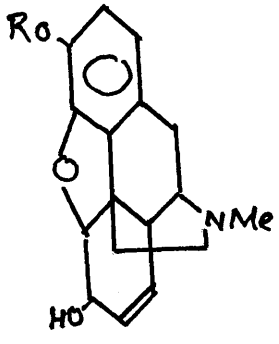
While attempts were being made to get over these difficulties in the above synthetic route to (LXlll; R = i-Pr),morphine

(LV) was isopropylated in the usual way by refluxing it with freshly distilled isopropyl iodide in methanolic potassium hydroxide under an atmosphere of nitrogen to afford 3-isopropyl morphine (LVI; R = i-Pr) (55% yield) which failed to crystallise but could be characterised as its picrate. isoPropyl morphine (LVI; R = i-Pr) was then oxidised to 3-isopropyl morphinone (L) (60% yield) by means of freshly prepared silver carbonate [28]. 3-isoPropyl morphinone (LVII; R = i-Pr) also failed to crystallise but was characterised as its picrate. isoPropyl morphinone (LVII; R = i-Pr) was successfully reduced with lithium aluminium hydride as well as sodium borohydride [29], [30] to afford a product whose picrate was identical (mixed m.p. and infra-red spectra) with the picrate of authentic 3-isopropyl morphine (LVI; R = i-Pr). The resulting 3-isopropyl morphine (LVI; R = i-Pr) was also deisopropylated successfully using pyridine hydrochloride to furnish material identical in every respect with authentic morphine [31]. Thus, morphine (LV) was reversibly converted into isopropyl morphinone (LVII; R = i-Pr) but as all attempts to improve the yields and quality of the various intermediates in the synthesis of laudanosoline-4':6-diisopropyl ether (LXIII; R = i-Pr) failed, we were forced to give up this apparently simple route for the synthesis of the desired phenolic

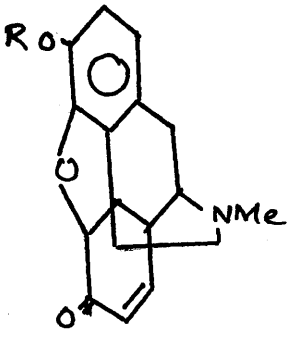
FLOW SHEET II



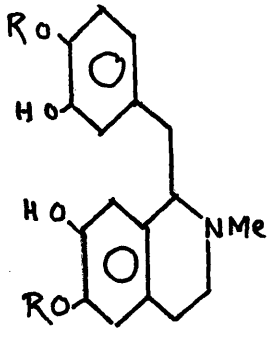
LV



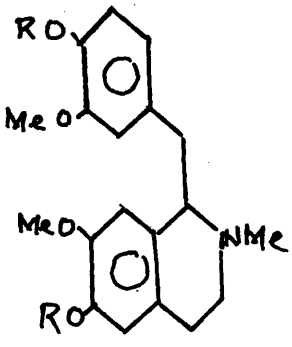
LVI



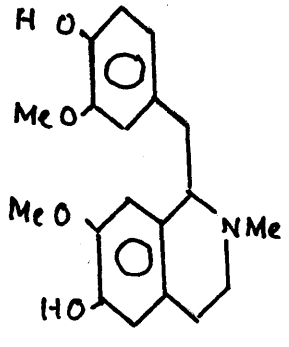
LVII



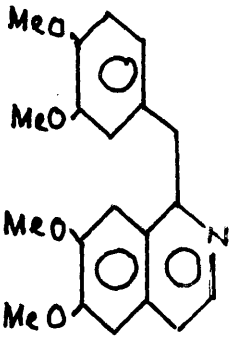
LXIII



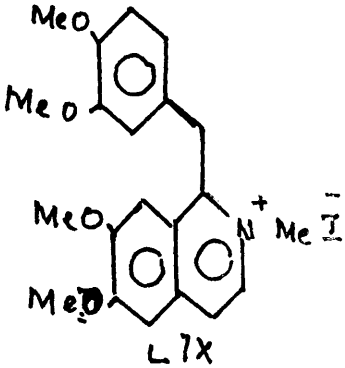
LXII



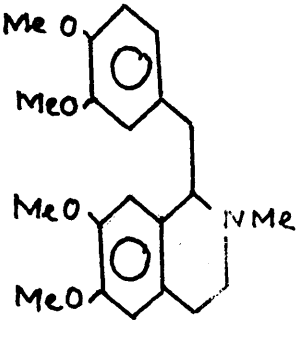
LXI



LVIII



LIX



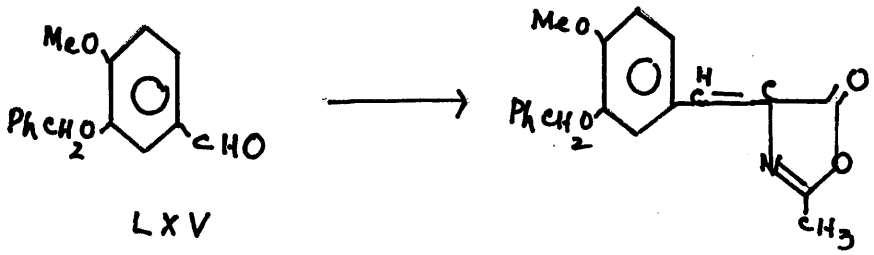
LX

precursor in favour of the rather long and 'classical' route outlined below.

Synthesis of laudanosoline-4':6-dimethyl ether (LXXVII) (see Flowsheet III). (p. 151A)

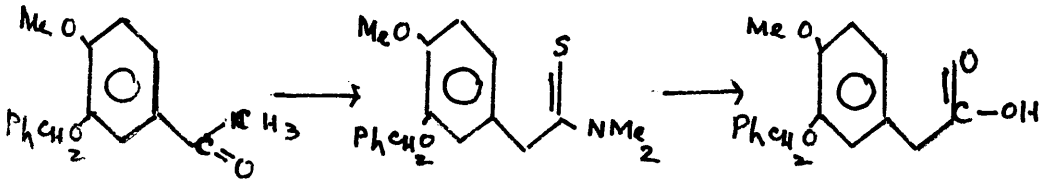
isoVanillin (LXIV) was benzylated in the usual way (75-85% yield) to give O-benzylisovanillin (LXV) which was converted into 3-benzyloxy-4-methoxyphenylacetic acid (LXVII) via 2-phenyl-4-(3'-benzyloxy-4'-methoxybenzylidene)-oxazolone (LXVI). This conversion proved to be somewhat more difficult than had originally been anticipated. The chief obstacle was the difficulty in synthesising large enough quantities of 3-benzyloxy-4-methoxyphenylacetic acid needed for this long synthesis. The usual method of synthesis of phenylacetic acids from aromatic aldehydes involves the intermediate preparation of phenyloxazolone by condensation with hippuric acid, the hydrolysis of this oxazolone with aqueous alkali and the perhydrol oxidative decarboxylation of the resulting phenylpyruvic acid. One is then faced with the problem of separating the desired phenylacetic acid from benzoic acid formed at the same time during the cleavage of the oxazolone. Attempts at separating it by treating the intermediate mixture before perhydrol oxidation with bisulphite or sulphur dioxide did not prove feasible and only a very small yield of the desired

pure phenylacetic acid was obtained. An alternative method of separation consisting of the preparation of methyl esters of the mixture of acids using sulphuric acid as a catalyst was attempted. Apart from the difficulty of preventing the partial hydrolysis of benzyloxy groups, under varying conditions of esterification tried which led to the formation of a tarry mixture, the separation of the esters by vacuum distillation of the more volatile methyl benzoate was not very satisfactory and the resulting methyl-3-benzyloxy-4-methoxyphenylacetate had to be purified by repeated crystallisation or by chromatography over alumina with the consequent fall in the overall yield of the desired acid. In addition, the ethyl esters were prepared in a similar manner but these offered no advantage in separation. Attempts were also made to effect the separation of the two acids by simple crystallisation and it was found that while a synthetic mixture of the two pure acids could be separated cleanly by crystallisation from 50% aqueous acetone, the acid mixture obtained after perhydrol oxidation could not be separated in this manner. In order to avoid this troublesome separation, another method was considered which would utilise acetylglycine in place of hippuric acid.



Many attempts were made to obtain the methyl oxazolone (LXXVIII). Varying the proportions of the reaction or the time of heating or the temperature at which the reaction mixture was heated did not succeed in preventing the mixture from becoming a tar. The difficulty of obtaining methyl oxazolone was probably due to the two centres of possible attack present in acetylglycine and resulting in the lack of a clean condensation possible with hippuric acid. Another route to 3-benzyloxy-4-methoxyphenylacetic acid was also explored though with little success. It utilised 3-benzyloxy-4-methoxy-ω-nitrostyrene, prepared in the usual way from O-benzylisovanillin by condensation with nitromethane in alcoholic sodium hydroxide, as the starting material. Attempts were made to reduce this compound by means of zinc dust to the corresponding aldoxime. Isolation of the aldoxime itself was found impractical as was the conversion of the aldoxime to nitrile and

hydrolysis of the nitrile to the acid without isolation of an intermediate. All of these compounds were obtained as very impure, viscous oils, which rapidly deteriorated. The Arndt-Eistert reaction utilising 3-benzyloxy-4-methoxy benzoic acid as a starting material was not considered in view of the large stocks of 3-benzyloxy-phenyl acetic acid needed for this synthesis and the possible hazards and impracticability of using diazomethane on such a large scale. The Wilgerodt-Kindler reaction involving the use of 3-benzyloxy-4-methoxy-acetophenone (LXXIX) as starting material did not seem to offer any obvious advantage over the familiar ozazolone method.



LXXIX

This method suffers from all the limitations that are undesirable from a preparative point of view [32]. Moreover, the starting material (LXXIX) needed for this route had to be prepared fresh while stocks of O-benzyl<u>iso</u>vanillin (LXV) had already been prepared.

In view of all these difficulties, the phenyl oxazolone method referred to already had to be explored in greater detail. It was found that the separation of benzoic acid and 3-benzyloxy-4-methoxy phenylacetic acid mixture resulting from the perhydrol oxidation of the intermediate mixture of the phenylpyruvic acid and benzoic acid was possible by careful chromatography over forty parts by weight of silica gel. After several preliminary experiments to standardise the conditions of the conversion of O-benzylisovanillin (LXV) into 3-benzyloxy-4-methoxyphenylacetic acid (LXVII) on a preparative scale, it was found that about twenty parts by weight of silica gel was the minimum that was needed to give a satisfactory separation of the acids. The time for which the oxazolone (LXVI) was heated with ten volumes of 10% aqueous sodium hydroxide, was critical as far as the yield of the desired phenylacetic acid was concerned. The longer the heating of the oxazolone with alkali, the poorer was the yield of the desired acid. This imposed a serious limitation on the scale on which the oxazolone cleavage could be done without undue losses in yield of the ultimate acid. The practical scale chosen for oxazolone cleavage was to reflux 50 grams of the oxazolone (LXVI) with alkali at a time when the evolution of ammonia gas could be brought to an end in about six to

seven hours. It was also found that the oxazolone cleavage step in the preparation of the phenylacetic acid was not quite straightforward. Careful chromatography of an acid mixture resulting from a relatively more drastic oxazolone cleavage led to the isolation of still another acidic material after the benzoic acid and the phenylacetic acid had been eluted. This acidic material, m.p. 97-8°C (from ethyl acetate) could not, however, be characterised conclusively although its spectroscopic data and analysis data seemed to suggest a close similarity to the phenylacetic acid. Repeated attempts to purify it by recrystallisation did not raise its melting point and there were definite depressions in melting points of the acidic material and some of its derivatives on admixture with the corresponding derivatives of the pure 3-benzyloxy-4-methoxyphenylacetic acid.

A stock of 3-benzyloxy-4-methoxyphenylacetic acid (LXVII) was consequently built up (over all yield from isovanillin was about 16%) by repeated runs following the phenyl oxazolone method involving the cumbersome and tedious chromatographic separation over silica gel. The benzoic acid was the first to be eluted (benzene containing 10% ether) and then came the desired 3-benzyloxy-4-methoxyphenylacetic acid (LXVII) with benzene containing 15% ether.

O-benzylvanillin (LXX) was prepared from vanillin (LXIX) by a method analogous to that for O-benzylisovanillin (LXV) (75-85% yield) and this was then converted into 3-methoxy-4-benzyloxy-ω-nitro styrene (LXXI) in the usual fashion by condensing nitromethane with benzylvanillin (LXX) in alcoholic sodium hydroxide (56% overall yield from vanillin) [33]. Initial attempts to prepare 3-methoxy-4-benzyloxy-ω-nitrostyrene (LXXI) by condensing nitromethane with benzylvanillin (LXX) in the presence of methylamine hydrochloride and sodium carbonate [34], [35], did not afford a satisfactory product in our hands and the product did not melt completely even at ca 160°C, although most of it melted at about 120°C. Lithium aluminium hydride reduction of 3-methoxy-4-benzyloxy-ω-nitrostyrene (LXXI) in refluxing ether afforded 2-(3-methoxy-4-benzyloxyphenyl)ethylamine (LXXII) (41% overall yield from vanillin). However, the extremely low solubility of the nitrostyrene (LXXI) in ether rendered the extension of this technique of reduction to the preparative scale impracticable and consequently the technique employing the addition of a solution of the ω-nitrostyrene (LXXI) in dry tetrahydrofuran to a suspension of lithium aluminium hydride in refluxing tetrahydrofuran was preferred. There was, however, no difference in the yields of the phenylethylamine

by the two techniques. Crystallisation of the phenylethylamine (LXXll) from ~~ether~~ light petroleum (40-60°) was not very feasible on a preparative scale and the phenylethylamine (LXXll) was used as such, after rigorous drying but without further purification; in the next stage of the synthesis although it was characterised in earlier experiments as the picrate and oxalate.

3-Benzyloxy-4-methoxyphenylacetic acid (LXVll) was converted into the acid chloride in the usual way by oxalyl chloride. No attempt was made to isolate and crystallise the acid chloride (LXVlll) which was immediately reacted with 2-(3-methoxy-4-benzyloxy phenyl)ethylamine in tetrahydrofuran solution in the presence of an equivalent amount of sodium hydroxide dissolved in the minimum amount of water. The resulting 3-benzyloxy-4-methoxy-N-2-(3-methoxy-4-benzyloxyphenyl)ethylacetamide (LXXlll) (11% overall yield from iso-vanillin) showed bands in the infra-red at 3270, 1640 and 1545 cm^{-1} (bonded "trans" secondary amide) 1260 and 1230 cm^{-1} (aromatic ether) in Nujol.

Cyclisation of 3-benzyloxy-4-methoxy-N-2-(3-methoxy-4-benzyloxyphenyl)ethylacetamide (LXXlll) with freshly distilled phosphorus oxychloride in boiling toluene afforded 1-(3-benzyloxy-4-methoxybenzyl)-6-

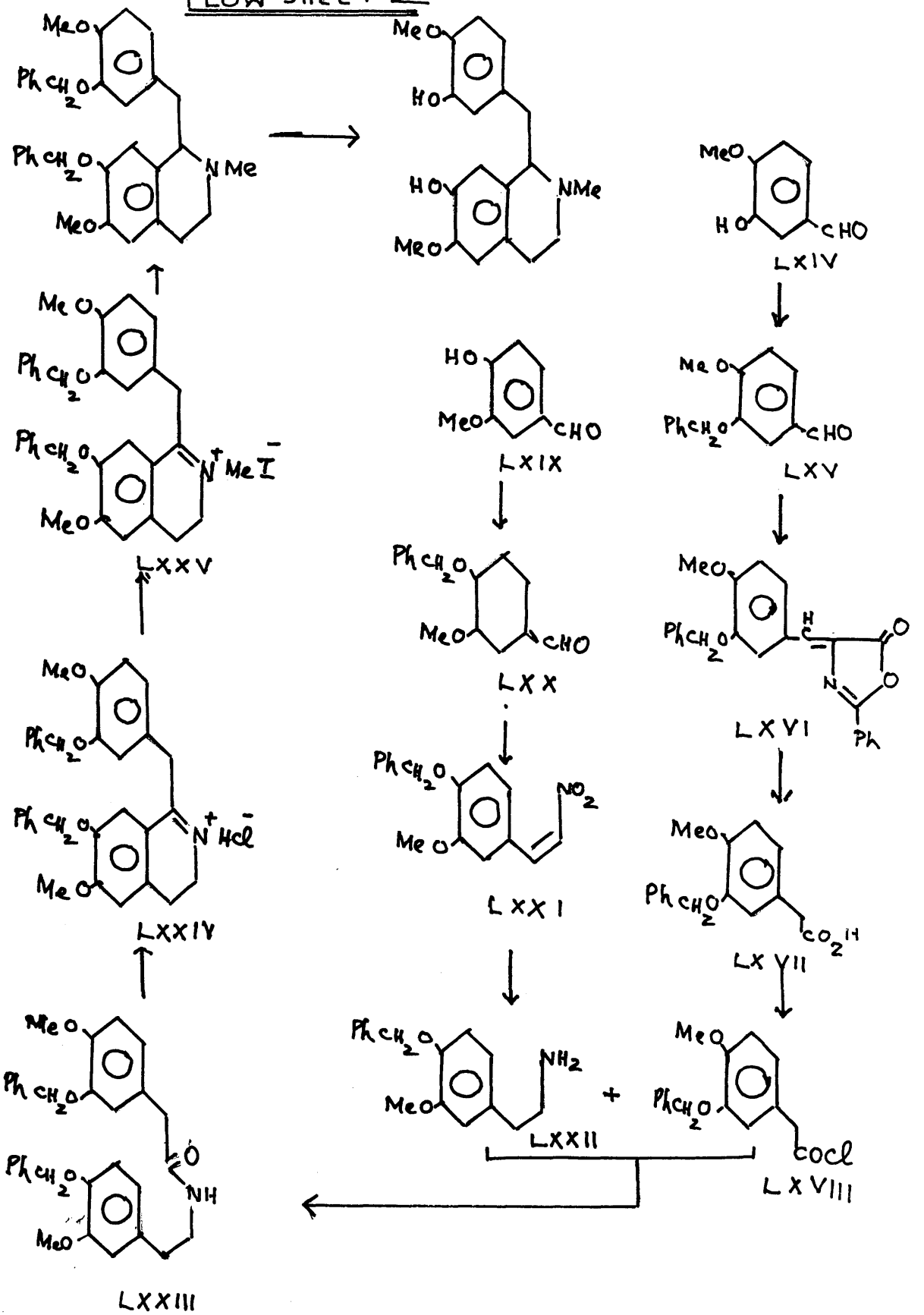
methoxy-7-benzyloxy-3:4-dihydroisoquinoline hydrochloride (LXXIV) (8.5% overall yield from isovanillin) which was decomposed with excess aqueous sodium bicarbonate and the resulting base immediately extracted with ether. The ether extracts, washed and dried over sodium sulphate were evaporated at low temperature under reduced pressure to get 1-(3-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline as a white amorphous powder which tended to turn yellowish on exposure to air. This base was immediately dissolved in dry benzene, the solution flushed with nitrogen and treated with methyl iodide to afford 1-(3-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline methiodide (LXXV) which was found to be labile and was therefore immediately reduced by sodium borohydride or potassium borohydride in the usual fashion to 1(3-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-2-methyl-1:2:3:4-tetrahydroisoquinoline (LXXVI), also characterised as the picrate (4.5% overall yield from isovanillin). Analogous borohydride reduction of quaternised salts has been frequently reported in the recent literature [36]. Several attempts to obtain laudanosoline-4':6-dimethyl ether (LXXVII) by catalytic hydrogenolysis of benzyloxy groups in 1-(3'-benzyloxy-4'-methoxybenzyl)-6-methoxy-7-benzyloxy-1:2:3:4-tetrahydro-2-methylisoquinoline (LXXVI) were unsuccessful. [37]

However, (LXXVI) could be smoothly hydrolysed to laudanosoline-4':6-dimethyl ether (LXXVII) by means of 25% hydrochloric acid in 3N acetic acid at 110-115°C (2-3% overall yield from isovanillin). Laudanosoline-4':6-dimethyl ether (LXXVII) could not be induced to crystallise and the attempts to prepare its oxalate, hydrobromide, hydrochloride, perchlorate etc., were equally unsuccessful. However, a picrate could be prepared in methanolic solution which, though never obtained in a good crystalline form, analysed correctly for laudanosoline-4':6-dimethyl ether picrate. The base regenerated from this picrate again failed to crystallise. However, methylation of the base with excess ethereal diazomethane in methanolic solution furnished a non-phenolic base identical in every respect with laudanosine prepared from papaverine in the manner outlined previously (page 139).

Attempts at the Oxidative Coupling of laudanosoline-4':6-dimethyl ether (LXXVII).

Several attempts have been made to oxidise laudanosoline-4':6-dimethyl ether (LXXVII) with alkaline potassium ferricyanide with a view to developing conditions suitable for its conversion into aporphine bases (XLVIII; R = Me) or (XLIX; R = Me) and/or the morphine type compound (L; R = Me) as already explained (page 134). The

FLOW SHEET III



attempted variations in experiments consisted of changes in the technique of adding the oxidant and/or the 'phenolic precursor', employing high dilutions for the reaction, varying the reaction times and alkalinity of the reaction medium, and so on. The various attempts made in this direction can be conveniently considered under the following heads.

a) Experiments involving the 'usnic acid technique' of Barton, Deflorin and Edwards [7], ie. adding a moderate excess of the oxidant, flushed continuously with oxygen-free nitrogen, to a well deaerated alkaline solution of the phenol being oxidised.

b) Experiments using the same 'usnic acid technique' but giving a very short time for the reaction and work up.

c) Experiments employing the 'simultaneous addition technique' wherein dilute solutions of the oxidant and the 'phenol', continuously flushed with oxygen-free nitrogen, were added simultaneously, slowly and at an equal rate, as far as possible, to a very dilute, well deaerated solution of the alkali.

d) Experiments involving the usual 'usnic acid technique' but using a large excess of an immiscible organic solvent in the reaction mixture so that the oxidation occufred mostly at the interface thereby preventing overoxidation of the phenol or the coupled product.

e) Experiment involving the 'Reverse Addition Technique' wherein a continuously deaerated benzene solution of the phenol was added slowly to a well-deaerated alkaline solution of potassium ferricyanide containing a large excess of the same organic solvent, benzene.

Before undertaking the oxidation of laudanosoline-4':6-dimethyl ether itself, several preliminary experiments on the recovery, separation and identification of known model aporphine bases like glaucine and corytuberine had to be carried out in order to find suitable conditions for the work up of oxidation mixture.

While a reasonable quantity of glaucine for this purpose was obtained through the courtesy of Dr. Manske to whom we are grateful corytuberine had to be extracted from Corydalis cava. The method employed for the extraction of corytuberine from Corydalis cava was essentially that employed by Manske and co-workers [38] with other

In experiments designed to demonstrate that tertiary nitrogen is not attacked under the conditions of ferricyanide oxidation, laudanosine was recovered unchanged. The author is grateful to Dr. A. Deflorin for this information.

complex oxidation mixtures with respect to the desired oxidation products, more still when the anticipated poor yield of such products in the presence of large amounts of undesirable products was considered. Paper chromatography and cellulose column chromatography were the obvious choice. Preliminary experiments on the behaviour of laudanosine, glaucine, methylated corytuberine etc. on paper showed that they had very close R_f values and their resolution from even simple authentic mixtures was not easy. This was further complicated by the occasional appearance of 'tails' and 'streaks'. Even preliminary experiments had to be done using fairly long strips (about 40 to 50 cm.) before any reasonable resolution could be achieved. After several trials with different solvent systems, different grades of paper and the various methods of treating these papers, it was found that the best conditions to obtain a reproducible, satisfactory resolution, free from 'streaking' and 'tailing', of these authentic mixtures consisted in using Whatman No.1 paper strip impregnated with $M/_7$ potassium dihydrogen phosphate and dried at room temperature. The best solvent system was found to be a mixture of 100 parts (by volume) of freshly distilled n-butanol, two parts of 'AnalaR' formic acid and twenty parts of distilled water, prepared twenty four hours

before use. The paper strips (ca. 50 cm. long) carrying the material to be resolved or chromatographed should be equilibrated with the same solvent for at least twenty four hours, before starting 'irrigating' them, in a sealed cabinet placed in a chamber maintained at 24°C. 'Irrigation' was continued for about twelve hours and then the paper strips were dried at room temperature in a fume cupboard before being developed with the modified Dragendorff reagent [40]. Attempts to resolve the authentic mixtures, on preparative scale, on a cellulose column (standard grade 'cellulose powder' Whatman) proved unsatisfactory, presumably due to the practical difficulty of treating the 'cellulose pulp' uniformly with aqueous M/7 potassium dihydrogen phosphate and yet retaining a suitable degree of hydration of the pulp on drying to give a firm and channel-free packing of column. Subsequently, resolution of the mixtures on thick Whatman 3MM paper was tried successfully.

Before we consider the results of the various oxidation experiments (see pp.197-207for details), it would be appropriate to state briefly the general outline of oxidation procedure that was ultimately followed after some initial promising results had been obtained. A moderate excess of potassium ferricyanide solution in

water (2.5 moles) was thoroughly flushed with oxygen-free nitrogen and then, maintained under a continuous atmosphere of nitrogen, it was run gradually into a well-stirred, very dilute solution of the phenol i.e. laudanosoline-4':6-dimethyl ether in 'AnalaR' ethylacetate (ca. 0.3 millimole per litre) suspended in a dilute solution of 'AnalaR' sodium bicarbonate in freshly boiled water which had already been thoroughly flushed with oxygen-free nitrogen and cooled to 0°C. The addition of the oxidant took about one and a half hours and the reaction stopped after an additional stirring for another one and a half hours. The deep green ethyl acetate phase, washed with a saturated solution of 'AnalaR' sodium chloride and dried over anhydrous sodium sulphate, was evaporated at low temperature (ca. 40-50°C) under reduced pressure and the resulting residue was methylated with excess ethereal diazomethane solution in the presence of a little methanol (one week in a refrigerator). The methylated product was streaked on 3MM paper strips (Whatman, 19 cm. wide and about 50 cm. long) and run with the solvent as already described. Initial experiments had shown that the oxidation mixture thus obtained consisted mostly of laudanosine, a little polymeric material which did not move much from the starting line and a faint spot with R_f value almost identical with that of authentic glaucine. The position of this faint spot on the

3 MM paper strips was located by means of control strips and the strips containing this glaucine like zone were eluted with absolute ethanol in a sealed chamber already saturated with ethanol vapours to prevent evaporisation of the ethanol front as it travelled on these strips. The eluted material was rechromatographed over 3 MM paper strips and the zone with glaucine like R_f value eluted again to get rid of any laudanosine that might have contaminated it. The uniformity of the eluted material was checked again by its behaviour on paper.

Results and Discussion

The material eluted from paper strips, as described above, had an R_f value 0.52 as compared with 0.50 of glaucine, 0.64 of methylated corytuberine and 0.58 of authentic laudanosine. However, the ultra violet spectrum of this material (see page 202) did not show the two maxima typical of glaucine and other aporphines. Rather, it was more like laudanosine with the difference that it showed some appreciable absorption in the region 295-320 mμ. The maximum at 280 mμ had almost the same intensity as in the case of laudanosine ($\sim$8,000). The infra-red spectra (thin film and carbontetrachloride

solution) were not very informative, the only significant bands being 2910, 1595, 1515, 1464, 1254, 1107, 1030 cm^{-1} (thin film) and 2910, 2840, 1530, 1460, 1214, 1115 cm^{-1} (carbontetrachloride).

Attempts to crystallise this material which was a light brown gum did not succeed, neither did attempts to prepare crystalline derivatives like hydrobromide, methiodide, picrate, oxalate, etc..

A few words about the results of other oxidation experiments would not be out of place at this point. All the various conditions tried for the oxidation did not yield the desired coupled products as examined spectroscopically and by paper chromatography. The main difficulty was that while attempts at mild oxidation by using potassium ferricyanide in less than theoretical amounts for short periods led invariably to the recovery of most of the parent phenol in the form of laudanosine, use of excess oxidant over longer reaction periods resulted in overoxidation of the initially coupled products furnishing complex polymers besides the unoxidised starting phenol recovered as laudanosine. It appears from this that the initial, simple coupled products of oxidation of aporphine type, once formed, are much more readily oxidised further than the starting phenolate anions also present in the reaction mixture at the same time. This conclusion seemed justified in view of the U.V. data on some of these oxidation mixtures. They

showed significant intensities of absorption in the 300 mμ region, sometimes of the same order as at 280 mμ, in contrast to the starting phenol, laudanosoline-4':6-dimethyl ether and the corresponding methylated base laudanosine, which exhibited only a single $\lambda_{max.}$ at about 280 mμ (log ε 3.1) with a sharp drop in intensity of absorption after 295 mμ (ε at about 300 mμ being only of the order of 600-700). These results appeared still more promising when it was found that in authentic corytuberine, methylated essentially under the conditions used for methylating the oxidation mixtures, the second peak at 305 mμ (log ε, 3.8) (before methylation) was practically reduced to a broad shoulder only (log ε at 300 mμ being 3.6) (after methylation). All this seemed to suggest that intramolecular coupling of (LXXVII) yielding aporphines has probably taken place to some extent but the appearance of a distinct maximum at about 300 mμ is masked by the presence of a large excess of other species also present or formed in the reaction mixture, it being assumed that the intermolecularly coupled products of oxidation, unlike the intramolecularly coupled ones, would essentially have the same pattern of U.V. spectra as the starting phenol or laudanosine. This was in agreement with the fact

that the intermolecularly coupled products, bisbenzylisoquinolines for example, have ultra violet absorption spectra very similar to that of the parent, uncoupled benzylisoquinolines. All attempts to evolve a happy compromise of conditions whereby the initial coupled products of oxidation are prevented from further oxidation and yet the parent phenol is oxidised in amounts sufficient to give a reasonable yield of the desired coupled products were, however, unsuccessful. In most of the experiments of this kind, the oxidation product consisted almost entirely of polymeric material which hardly moved on paper and/or the unoxidised starting phenol. Equally unsuccessful were the attempts to enrich the oxidation mixtures with respect to the small yield of the desired oxidation products, possibly formed during oxidation experiments carried out for a brief period, with the help of paper chromatography or other methods.

It has already been pointed out in Chapter I that the initial stage of the ferricyanide oxidation of phenols is the reversible reaction between phenolate anion and the ferricyanide ion giving ferrocyanide ion and a mesomeric aryloxy radical. Irreversible reactions then follow giving mixture of dimeric and polymaterial products. Laudanosoline-4':6-dimethyl ether (LXXVII) has already been

illustrated in different equivalent forms (see page 134) and would, on oxidation, presumably furnish the corresponding mesomeric aryloxy radicals which could then suffer the various possible changes already referred to in Chapter I. Apparently, there is a wide variety of possible types of union giving self-coupled products, even if we assume that 'carbon-carbon' coupling would be most important. This situation is complicated still further when we remember that the phenol laudanosoline-4':6-dimethyl ether (LXXVII) contains more than one ortho- and para positions which are free for coupling. In addition, simple changes like hydroxylation of the parent phenol, oxidation of the tertiary amino group present to N-oxide or simple N-demethylation [41] cannot be ruled out and these appear to be particularly important in the present case where the oxidation product is spectroscopically so similar to authentic laudanosine. Last but not least is our limitation as compared with Nature in inducing molecules to behave in a specific way. One only wonders at the way Nature manages to synthesise altogether different, structurally, but biogenetically related molecular species in the same plant. It would suffice to recall just one instance of Cocculus laurifoluis DC. where coclaurine, coclanoline [(≡ laudanosoline-4':6-dimethyl ether (LXXVII)], laurifoline (LII),

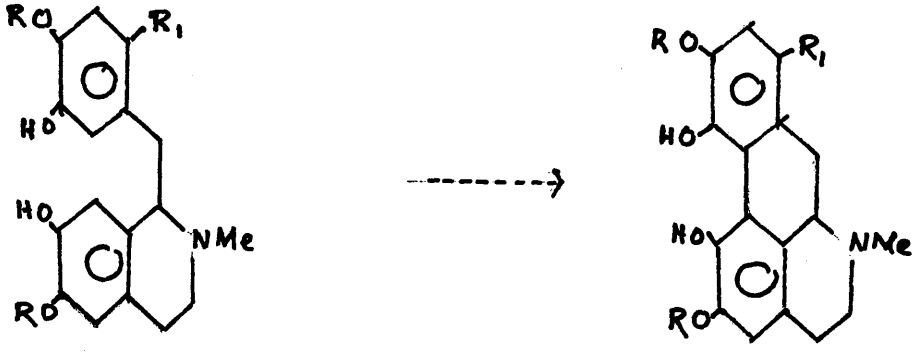
magnoflorine (LIII), dihydroerysodine (an erythrina alkaloid), trilobine (a bisbenzylisoquinoline), have been found to occur together. It is still a mystery how Nature manages this formidable task although we generally tend to console ourselves by saying that "in the living cell phenol dehydrogenations are caused in a highly organised surrounding by enzymes and it is probable that reacting phenol molecules become suitably oriented so as to make a directed coupling possible, thus minimising formation of by products".

In view of all this, it is no wonder that we have not been successful so far in imitating Nature. If the plant really synthesises morphine and aporphine alkaloids by the oxidative coupling of some precursor like (LXXVII), the human attempts to achieve some sort of orientation by adsorbing phenols on surfaces, or by incorporating them in thin films, e.g. foams or by working with emulsions or in high dilutions are apparently too crude and the realisation of this ideal through such arbitrary methods would be a highly fortuitous thing.

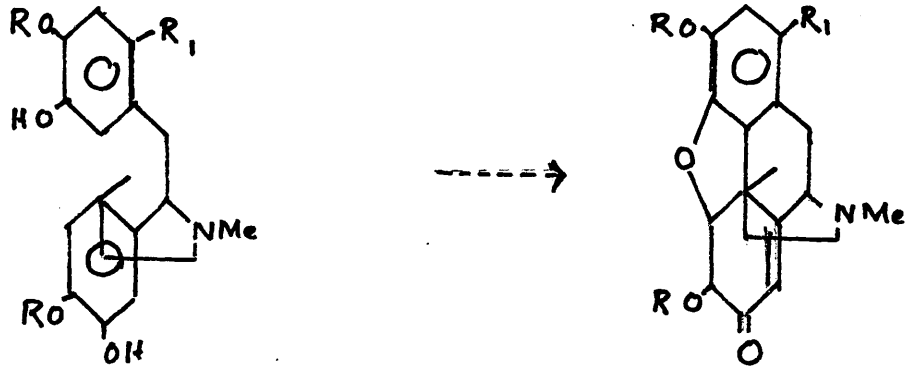
A comparison of laudanosoline-4':6-dimethyl ether (LXXVII) with some of the phenolic compounds like C-methylphloroacetophenone which have been subjected to successful oxidative coupling yielding natural products shows that while in methylphloroacetophenone all the

nuclear positions but one ortho to a hydroxyl are substituted, laudanosoline-4':6-dimethyl ether has quite a few nuclear positions, ortho and para to hydroxyl, which are free to suffer coupling.

It may be reasonable to expect that the substitution of (LXXVll) by a phenol, say (LXXX), in which all the free ortho and para positions, except the ones where coupling is desired, are blocked, preferably by substituents which can be subsequently removed, might make a directed intramolecular coupling more likely. A phenol like (LXXXl) may be expected to give a reasonable yield of the morphine type coupled product:



LXXX

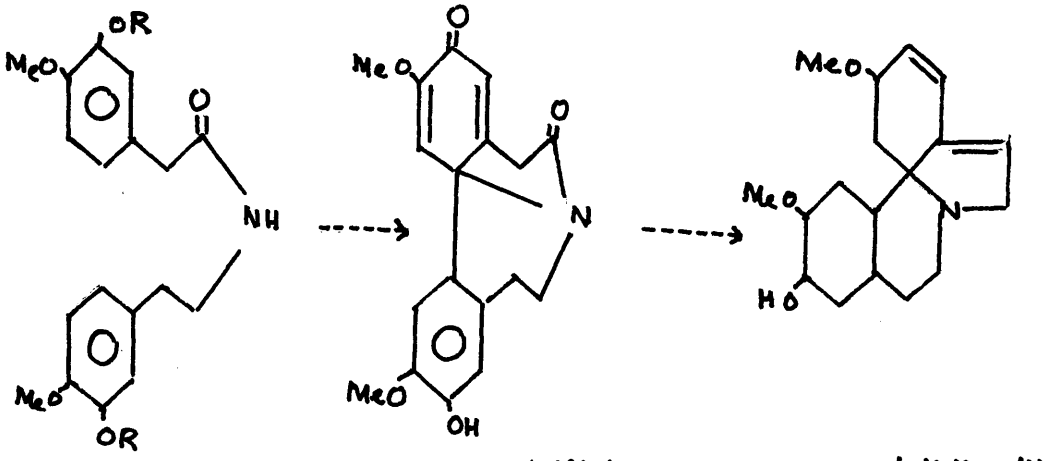


LXXXI

But it is still questionable how easy the preparation of these alternative phenolic precursors in quantity would be so that the validity of the hypothesis of oxidative coupling for the biogenesis of morphine and aporphine alkaloids could be tested.

Attempted Biosynthesis of Erythrina Alkaloids. *

It has already been explained in Chapter II how a phenol like (LXXXII; R = H) could give rise to erysovine (LXXXIV), an 'aromatic' erythrina alkaloid, through oxidative coupling.



LXXXII LXXXIII LXXXIV

3-Benzyloxy-4-methoxyphenylacetyl chloride, prepared in the usual way from isovanillin, was reacted in tetrahydrofuran solution with

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* This work was done in this laboratory by Dr. J. E. Stouffer and the author is grateful for his kind permission to reproduce here a summary of his results.

2-(3-benzyloxy-4-methoxyphenyl)ethylamine, obtained from vanillin via 3-benzyloxy-4-methoxy-ω-nitrostyrene, to afford O-benzylhomoisovanillo-β-(3-benzyloxy-4-methoxyphenyl)ethylamide (LXXXll; R = CH_2Ph) which was converted into homoisovanillo-β-(3-hydroxy-4-methoxyphenyl)ethylamide (LXXXll; R = H) by the hydrogenolysis of the protecting benzyloxy groups with 10% palladised charcoal in methanol containing a few drops of concentrated hydrochloric acid. Lithium aluminium hydride reduction of (LXXXll; R = H), using dioxan as a solvent, gave the corresponding amine as an impure, viscous oil which rapidly deteriorated.

The oxidation of the amide (LXXXll; R = H) was attempted under a variety of conditions. The technique of adding simultaneously an aqueous solution of potassium ferricyanide and a methanolic solution of the phenol to a rapidly stirred solution of sodium carbonate was employed. Variations of temperature from 0° to room temperature and the pH from 7 to 10 did not give any different results. A polymeric material, insoluble in all solvents and having a decomposition temperature above $300^{\circ}C$, was obtained in each case beside a small amount with a small peak in the ultraviolet absorption spectrum at 282 mμ corresponding to phenolic absorption.

Attempted air oxidation and coupling at 100°C for seven hours afforded a product whose infra-red spectrum was not significantly different from that of starting material.

Another oxidation experiment carried out at pH 5-6 yielded a viscous gummy product from which a crystalline substance, m.p. 126° had an infra-red spectrum identical with that of (LXXlll; R = H).

It has been suggested, however, that while the oxidative coupling of the amide (LXXXll; R = H) has not been very promising, further work with the corresponding amine might be more fruitful.

EXPERIMENTAL

ATTEMPTED SYNTHESIS OF LAUDANOSOLINE-4':6-DIISOPROPYL ETHER* (See Flowsheet II, page 141A) (LXIII; R = i-Pr).

Papaverine methiodide (LIX).

Papaverine (LVIII) was converted into papaverine methiodide by Awe and Unger's method [27]. Pale white prisms (from absolute ethanol), m.p. 194-195°C (85% yield).

Laudanosine (LX).

Papaverine methiodide (LIX) was reduced by Awe and Unger's method [27] to give in 40% yield (cf. Awe and Unger) laudanosine. Colourless needles (from aqueous ethanol), m.p. 114°C.

Demethylation of Laudanosine with Aluminium Chloride.

A mixture of laudanosine (20 g.), pale yellow, twice sublimed aluminium chloride (50 g.) and twice distilled nitrobenzene (200 c.c.) was heated under good stirring, in a bath maintained at 80°C, for two hours. The cooled reaction mixture was poured into a solution of 6N. sulphuric acid (80 c.c.) and water (720 c.c.) shaken vigorously until

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Footnote * The author gratefully acknowledges the collaboration of Dr. T. Cohen in the attempted synthesis of laudanosoline-4':6-diisopropyl ether.

a thick white emulsion was formed. This emulsion was then extracted with ether (1.5 litres in four portions) to remove nitrobenzene. To the remaining aqueous phase was added tartaric acid (100 g.), with stirring. Ammonia was added to neutrality and then hydrazine (50% aqueous solution) was added carefully to maximum cloudiness (pH about 8.5). The milky mixture was then exhausted with ether (1.8 litres in eight portions). Evaporation of the washed and dried (sodium sulphate) extracts under reduced pressure afforded a light brown oil which was taken up in warm 48% hydrobromic acid (100 c.c.). After three days at room temperature, 4.4 g. of a buff coloured solid was collected which melted at about 164° over a large range and the melt was never quite clear. The mother liquor, diluted with an equal volume of water, deposited after two days a solid (2.2 g.) which melted at about 154° over a large range. The mother liquor obtained from the second crop was diluted again with water and left in the refrigerator when 2.3 g. of a solid melting at about 157° was deposited after six days. Thus a total yield of 8.9 g. of the hydrobromide (38% yield, it being assumed that it was entirely the hydrobromide of laudanosoline-3':7-dimethyl ether). On recrystallisation from 50% aqueous methanol, a great loss in yield was encountered and the

precipitation was exceedingly slow. Each such recrystallisation raised the melting point but a constant melting sample could never be obtained. The highest melting sample obtained after six recrystallisations had the melting point of 175° with a wide range. (Found: OMe, 14.20. $C_{19}H_{24}O_4NBr$ requires OMe, 15.12; $C_{19}H_{24}O_4NBr.H_2O$ requires OMe, 14.49).

This data, however, does not tell conclusively the nature of the hydrobromide, and it appears that the hydrobromide obtained above is a mixture of the hydrobromides of the different isomeric laudanosoline dimethyl ethers that are theoretically possible on demethylation of laudanosine.

When the demethylation of laudanosine was repeated under conditions given above, the yields obtained in different experiments were not consistently uniform. In fact, they varied from 5% - 35% and every time the product did not have any sharp melting range. Several attempts were made with somewhat modified conditions but with no useful results, even when the different reagents used were ensured to be of highest purity. Schöpf and Thierfelder [25] have, however, reported a 50% yield of laudanosoline-3':7-dimethyl ether by demethylating laudanosine under the conditions given above.

Isopropylation of the Product obtained above after the demethylation of Laudanosine.

To a solution of potassium hydroxide (7.70 g.) in methanol (80 c.c.), previously deaerated by bubbling oxygen-free nitrogen through it, was added under nitrogen, the hydrobromide of the laudanosoline ether obtained above (5.88 g.) and isopropyl iodide (28 g.) which had been previously washed with sodium bisulphite solution and dried over calcium sulphate. The mixture was refluxed for $3^{1}/2$ hours when the pH of the reaction mixture was about 7. The supernatant liquid was decanted and the residue combined with that obtained after evaporating the decantate under reduced pressure. The combined residues were equilibrated between normal sulphuric acid and ether. The acidic aqueous layer was extracted twice again with ether. The combined ether extracts (A) were set aside. The remaining acidic aqueous phase was basified with ammonia and finally with dilute sodium hydroxide (pH about 10), and the mixture immediately extracted with ether. The ether extracts (B), washed and dried over potassium carbonate, left, on evaporation under reduced pressure a light brown oil (4.5 g.). A part of this oil (4.39 g.) was converted into styphnate in ethanolic solution when an orange solid, m.p. 126-32°,

(5.29 g.). After six recrystallisations from ethanol, only 0.8 g. of the styphnate (orange needles), m.p. 189-90°C, was obtained, (8% yield calculated on the basis of laudanosoline-3':7-dimethyl ether hydrobromide).

	C	H	N	AgI/Sample
Found	56.50	5.53	8.82	1.38
$C_{31}H_{38}O_{12}N_4$ requires	56.50	5.81	8.51	1.43

All attempts to crystallise the colourless oil obtained by decomposing the above styphnate, m.p. 190°C, were unsuccessful.

No improvement in yield or quality resulted when the reaction was carried out in tertiary butyl alcohol in the presence of potassium tert-butoxide.

However, when this isopropylation was repeated with later samples of 'laudanosoline-3':7-dimethyl ether hydrobromide, even the small yield of styphnate obtained above disappeared and only insoluble, brown tars were obtained. This isopropylation could not be repeated under the most diverse conditions while every effort was made to establish the purity of different reagents before use in the reaction.

Attempted Selective demethylation of the supposed laudanosoline-3':7-dimethyl-4':6-diisopropyl ether obtained above. [26]

a) The styphnate (crude, m.p. 127-131°C) obtained above was decomposed with concentrated ammonia to give, after the usual work up, a viscous, pale yellow oil (3.24 g.).

To a mixture of this oil, liquid ammonia (400 c.c.) and ether (100 c.c.) was added sliced sodium (5 g.). The whole mixture was left in a Dewar flask fitted with a potassium hydroxide tube for 22 hours. The blue colour of sodium was then discharged with ethyl acetate-ether, followed by ethanol-ether, ethanol, water-ethanol and finally water. The aqueous phase was diluted with water to about 300 c.c., the resulting yellow aqueous phase separated from the organic phase and extracted four times with ether. The extracts (washed and sodium sulphate dried) were evaporated under reduced pressure to furnish a non-phenolic viscous oil (0.46 g.) which was converted into a styphnate which melted at 146-48°C after two crystallisations.

The aqueous phase was then made slightly acidic with 6N sulphuric acid and pH was then adjusted to about 8.5 by careful addition of hydrazine hydrate solution. The resulting cloudy mixture was extracted with methylene chloride to afford, on evaporation of the sodium

sulphate dried extract, a pale yellow viscous oil (2.65 g.). A part of this oil (2.22 g.) was dissolved in ethanol and mixed with styphnic acid (1.42 g.). The clear yellow solution was evaporated on a steam bath and allowed to crystallise overnight. The resulting mass was mixed with some ethanol and filtered to give a yellow solid (1.22 g.), m.p. 138-42°. This solid was resolved into two fractions by a careful fractional crystallisation from ethanol. The crude solid (1.22 g.) was boiled with excess ethanol, cooled and filtered. The filtrate (A) was set aside while the solid (0.18 g.) melted at 140-44°C. One crystallisation from 95% ethanol gave yellow plates m.p. 181-84°C (caused considerable depression on admixture with authentic styphnic acid). An analytical sample, m.p. 185-87°C was obtained after two crystallisations.

	C	H	N	AgI/sample
Found	55.63	5.81	9.48 9.30	1.067
$C_{30}H_{36}O_{12}N_4$ requires (2-isopropoxy and 1-methoxy groups).	55.89	5.63	8.69	1.092

[Previous experience with model compounds had shown that all the isopropyl iodide did not come over].

The filtrate (A) was concentrated and allowed to crystallise when a yellow solid (135-43°) (0.84 g.) was obtained which on successive crystallisations from 95% ethanol yielded a solid, m.p. 143-45° which did not however appear uniform under the microscope. Repeated crystallisations raised the melting point to 145-47°C. (Kofler block). The micro m.p.'s of this solid showed great fluctuations when heated on the Kofler block. Sometimes it remained unmelted even up to 180°.

	C	H	N	AgI/Sample
Found	56.13 56.03 56.04	6.43 5.42 5.64	8.78	1.043
$C_{30}H_{36}O_{12}N_4$ requires	55.89	5.63	8.69	1.092

b) The pure styphnate, m.p. 189-90.5°, of the supposed laudanosoline-3':7-dimethyl-4':6-diisopropyl ether (LXll; R = i-Pr) was decomposed with concentrated ammonia as usual to give a colourless oil (0.73 g.) which was dissolved in anhydrous ether (15 c.c.) and mixed with liquid ammonia (90 c.c.) in a Dewar flask. Sodium slices (1.17 g.) were added to this mixture and the flask was closed to atmosphere by a potassium hydroxide tube. This was worked up as above to afford an oil (0.48 g.) from the phenolic fraction which, however, failed to give

any styphnate or picrate even when its styphnic acid solution was seeded with a crystal of the styphnate crystals described above.

The non-phenolic fraction gave a brown, viscous oil (0.17 g.) which formed a styphnate (0.16 g.) m.p. 155-58°C. This styphnate could again be separated into two portions: the more insoluble one was in the form of pale orange rods, m.p.181-84°C (no depression on mixture with the styphnate of the starting material), the more soluble portion was in the form of plates,m.p. 157-60°C. The I.R. spectrum of this was identical with that of the styphnate of the starting material except for a strong band at 3400 cm^{-1}.

	C	H	N	AgI/Sample
Found	56.66	5.56	8.93	1.073
$C_{31}H_{38}O_{12}N_4$ requires	56.54	5.80	8.51	1.43
$C_{30}H_{36}O_{12}N_4$ requires	55.89	5.63	8.69	1.092

As all attempts to repeat the isopropylation step (LXl) to (LXll) in the above synthesis of laudanosoline-4':6-diisopropyl ether (LXlll; R = i-Pr) were unsuccessful and in view of ambiguous nature of the results of demethylation of laudanosine, the above route had to be abandoned in favour of the unambiguous, though long and cumbersome route to the synthesis of laudanosoline-4':6-methyl ether. (LXXVll; see Flow-sheet III, p. 181).

3-isoPropyl morphine (LVI; R = i-Pr).

A solution of potassium hydroxide (0.85 g., 0.015 mole) in methanol (40 c.c.) contained in a 100 ml. three-necked flask fitted with a reflux condenser, a mechanical stirrer and an inlet tube for nitrogen was flushed with oxygen-free nitrogen for fifteen minutes. To this solution, while nitrogen was still passing, morphine (1.45 g., 0.005 mole) and freshly distilled isopropyl iodide (3.5 g., 0.02 mole) were added and the mixture refluxed gently, under good stirring and a constant atmosphere of nitrogen, for three and a half hours. The reaction mixture was concentrated, as much as bumping would permit, under reduced pressure, the residue taken up in 1N. sodium hydroxide and the resulting milky solution thoroughly extracted with chloroform (250 c.c. in 5-6 instalments). The extract, washed and dried (potassium carbonate), was evaporated under reduced pressure to yield a viscous, yellow oil (1 g.) which failed to crystallise. However, it gave a picrate (50% overall yield from morphine) in methanolic solution. Rectangular rods (from ethanol), m.p. 184-85°C.

	C	H	N
Found	56.40	5.20	10.23
$C_{26}H_{28}O_{10}N_4$ requires	56.11	5.07	10.07

Attempts to crystallise the 3-isopropylmorphine liberated from the picrate in the usual way were also unsuccessful.

3-isoPropyl morphinone. (LVll; R = i-Pr).

Silver carbonate was prepared by Rapoport's method [28].

3-Isopropyl morphine picrate was decomposed in the usual way to get a yellow, viscous oil (3.5 g.) which was thoroughly dried and dissolved in 'AnalaR' benzene (65 c.c.). This solution of 3-isopropyl morphine was transferred to a three-necked flask fitted with a mechanical stirrer, an inlet tube for nitrogen and a liebig condenser set up for distillation. About 17 c.c. benzene was distilled off and then the condenser was changed into the reflux position. The solution was then flushed with oxygen-free nitrogen (15 minutes) and freshly prepared silver carbonate (14.76 g.) was introduced quickly. The mixture was refluxed gently for one hour, an efficient stirring and a constant atmosphere of nitrogen being maintained throughout.

The mixture was filtered hot, residue washed with hot benzene (2 x 25 c.c.). The combined filtrates were evaporated under reduced pressure to furnish a dark, red viscous gum (2.6 g.) which resisted all attempts at crystallisation. However, it could be converted into a picrate in methanolic solution. The separation of the picrate was rather delayed and there were considerable losses in yield on recrystallisation. 3-isoPropyl morphinone picrate was obtained as thin plates (from ethanol), m.p. 192-94°C. (dec.). On admixture with the picrate with the authentic 3-isopropyl morphine picrate, there was a depression of 20°C. $\nu_{max.}$ 1677 cm.$^{-1}$ (Nujol).

The analytical sample was prepared from ethylacetate/methanol (2:1).

	C	H	N
Found	56.23	4.85	10.22
$C_{26}H_{26}O_{10}N_4$ requires	56.31	4.73	10.10

Lithium aluminium hydride reduction of 3-isoPropyl morphinone.

(LVll; R = i-Pr) [29].

To a suspension of lithium aluminium hydride (0.5 g.) in dry ether (50 c.c.) was added a solution of 3-isopropyl morphinone (0.5 g.), cut back from its picrate as usual, in dry ether (50 c.c.). Addition of the isopropyl morphinone (LVll; R = i-Pr) was completed at such a rate that a gentle refluxing was maintained throughout. A slight warming in the initial stages was also necessary to start refluxing. When all the morphinone had been added (about one and a half hours) the mixture was refluxed for an hour more. On cooling the excess lithium aluminium hydride was destroyed by careful addition of water followed by the addition of excess 10 N. sodium hydroxide (200 c.c.), and the ether phase separated. The heavy, white precipitate of aluminium salts was repeatedly digested with ether. The combined ether extracts, washed and dried as usual, gave on evaporation a pale yellow viscous oil (0.34 g.) which was converted into a picrate. Recrystallised from ethanol, the picrate melted at 182-83°C. and showed no depression on admixture with the authentic picrate of isopropyl morphine. The identity of the two picrates was further confirmed by their infra-red spectra in Nujol which were practically superimposable.

Sodium borohydride Reduction of 3-isopropyl morphinone. (LVll; R = i-Pr) [30].

Sodium borohydride (0.55 g.) was slowly added to a well-stirred suspension of isopropyl morphinone (0.208 g.) in methanol (25 c.c.). The mixture was stirred for one hour more and then left overnight. The resulting solution was concentrated, as much as possible, under reduced pressure. The residual mixture was taken up in 10% aqueous sodium hydroxide (20 c.c.) and the turbid mixture thoroughly extracted with chloroform. The chloroform extracts, washed and dried as usual, gave on evaporation, under reduced pressure, a pale yellow viscous mass (161 mgs.) which gave a picrate 181-83°C, identical in all respects with that of authentic isopropyl morphine.

Deisopropylation of 3-isopropyl morphine (LVl; R = i-Pr) to morphine (LV). [31].

A mixture of 3-isopropyl morphine (0.498 g.) and pyridine hydrochloride (1.5 g.) was heated for fifteen minutes in Wood's metal bath maintained at 200°C. An atmosphere of oxygen-free nitrogen was maintained in the reaction flask throughout. The reaction mixture, at the end of fifteen minutes, was cooled immediately, dissolved in distilled water (10 c.c.), made alkaline with 4N sodium hydroxide and the brownish black mixture thus obtained was extracted with chloroform.

The pH of the remaining brownish aqueous phase was immediately adjusted to about 8 and cooled in a refrigerator. No solid separated except a dark brown gel like mass. Some ammonium sulphate (1 g.) was added and the mixture extracted with a mixed solvent chloroform ethanol (3:1). The extract left on evaporation a residue (220 mgs.) which was dissolved in methanol, passed through a column of grade '5' alumina and eluted with a large excess of methanol. The residue obtained on evaporating these eluates was sublimed under high vacuum when a white sublimate was obtained at $180^{\circ}C/2.15 \times 10^{-3}$mm., which melted at $240\text{-}45^{\circ}C$. (dec.) in an evacuated capillary tube. Recrystallisation from methanol raised the melting point to $253\text{-}54^{\circ}C$., undepressed on admixture with an authentic specimen.of morphine. The identity of the two samples was further confirmed by superimposable infra-red spectra (Nujol) and similar optical rotations $[\alpha]_D = 136.3$ (C = 0.22) cf. $[\alpha]_D$ authentic $= -133.3^{\circ}$ (C = 0.24) .

SYNTHESIS OF LAUDANOSOLINE-4':6-DIMETHYL ETHER. (LXXVII) (See Flowsheet III, page ISIA).

O-Benzylisovanillin (LXV).

Isovanillin (LXIV) was benzylated by Späth, Ovechoff and Kuffner's method [42] to give in 75-85% yield O-benzylisovanillin. Stout prisms (from ether-light petroleum 40-60°), m.p. 63-64°C.

2-Phenyl-4-(3'-benzyloxy-4'-methoxybenzylidene)oxazolone (LXVI)

O-benzylisovanillin (LXV) was converted into 2-phenyl-4-(3'-benzyloxy-4'-methoxybenzylidene)-oxazolone (LXVI) essentially according to the method of Robinson and Sugasawa [2] in a yield varying from 60-65% calculated on the basis of O-benzylisovanillin. Glistening yellow prismatic needles (from acetic acid 'AnalaR'), m.p. 159-60°C.

3-Benzyloxy-4-methoxyphenylacetic acid (LXVII)

It was prepared from 2-phenyl-4-(3'-benzyloxy-4'-methoxy benzylidene)-oxazolone (LXVI) via 3-benzyloxy-4-methoxyphenylpyruvic acid which was, however, not isolated during this conversion. The following method was found after several trials to give the best yields (30-40%, calculated on the basis of the oxazolone) of 3-benzyloxy-4-methoxyphenylacetic acid (LXVII). The scale of the oxazolone cleavage was rather critical as far as the ultimate yield of the

phenylacetic acid was concerned.

A mixture of 2-phenyl-4-(3'-benzyloxy-4'-methoxybenzylidene)-oxazolone (LXVI) (50 g.) and 10% aqueous sodium hydroxide solution (500 c.c.) was refluxed gently under an atmosphere of nitrogen till the evolution of ammonia gas ceased (6-7 hours). The resulting dark brown solution was saturated with carbondioxide gas (pH 8-8.5) and cooled to -5°C. An aqueous solution of hydrogen peroxide (6%) (250 c.c.) was then added slowly, under good stirring, at such a rate that the temperature of the reaction mixture did not rise above 5°C during the perhydrol addition. When all the hydrogen peroxide was added (about 40 minutes), the mixture was allowed to stand overnight in a refrigerator (14 hours). The mixture was then carefully acidified with conc. hydrochloric acid and the precipitated gummy acid mixture thoroughly extracted with chloroform. The chloroform extracts, washed and dried as usual, were evaporated under reduced pressure to yield a brown, viscous oil (ca. 45 g.) which was dissolved in the minimum amount of benzene and carefully chromatographed over silica gel (B.D.H.) (900 g.). Benzoic acid was the first significant fraction to be eluted off the column with benzene containing 10% ether. 3-Benzyloxy-4-methoxy phenylacetic acid came next with benzene containing 15% ether.

This desired phenylacetic acid was collected from the column carefully in a number of fractions as it was followed after some time by an oily fraction and had to be cut away from this oily portion carefully. The solid phenylacetic acid thus obtained from the eluates (benzene containing 15% ether) was recrystallised from benzene to get rhombic plates (13 g.), m.p. 127-29°C (mixed m.p. with authentic benzoic acid 90-125°C.).

An experiment involving the cleavage of 2-phenyl-4-(3'-benzyloxy-4'-methoxybenzylidene)-oxazolone (200 g.) at a time gave besides benzoic acid and a comparatively small yield of pure 3-benzyl oxy-4-methoxyphenylacetic acid (LXVll) a small amount of still another acidic material which could be crystallised, though not entirely satisfactorily, from most organic solvents like ethanol, ethylacetate, acetone/petroleum ether, acetic acid etc., m.p. 97-98°.

O-Benzylvanillin (LXX)

Vanillin (LXlX) was benzylated essentially by Finkelstein's [43] method to give in 75-85% yield O-benzylvanillin (LXl). Rhombic plates (from ethanol), m.p. 63-64°C.

3-Methoxy-4-benzyloxy-ω-nitrostyrene (LXXI).

O-Benzylvanillin (LXX) was converted into 3-methoxy-4-benzyloxy-ω-nitrostyrene (XXI) by Lange and Hambourger's method [33]. However, while Lange and Hambourger record a yield of 97%, we, in agreement with Finkelstein [43] could not get a yield of the crystallised product better than 65%. Moreover, when this preparation was repeated on a larger scale, the yield of recrystallised 3-methoxy-4-benzyloxy-ω-nitrostyrene (LXXI) averaged only between 50-60%, calculated on the basis of O-benzylvanillin.
Prismatic needles (from ethanol), m.p. 122-23°C.

2-(3-Methoxy-4-benzyloxyphenyl)ethylamine (LXXII).

3-Methoxy-4-benzyloxy-ω-nitrostyrene (LXXI) was reduced in the usual way to 2-(3-methoxy-4-benzyloxyphenyl)ethylamine (74% yield) by soxhletting the nitrostyrene into a suspension of lithium aluminium hydride in dry ether. However, the ω-nitrostyrene (LXXI) was practically insoluble in ether and this technique of reduction took extremely long time even on very small scale experiments. Consequently, Finkelstein's method [43] was preferred to prepare 2-(3-methoxy-4-benzyloxyphenyl)ethylamine (LXXII) from 3-methoxy-4-benzyloxy-ω-nitrostyrene (LXXI) (74% yield) calculated on the basis of the nitrostyrene.

The crude phenylethylamine (LXXII) obtained above was evaporated repeatedly in dry benzene under reduced pressure and used as such without any further purification by crystallisation from ether-light petroleum (40-60°). However, its purity was occasionally checked by transformation into its picrate (m.p. in an evacuated capillary being 174-175°C) and oxalate (m.p. 162-63°C).

3-Benzyloxy-4-methoxyphenylacetyl chloride (LXVIII)

3-Benzyloxy-4-methoxyphenylacetic acid (LXVII) (3.25 g.), suspended in dry ether (100 c.c.) was mixed with oxalyl chloride (8 c.c.) and the mixture refluxed gently on a water-bath. The acid gradually dissolved to yield a yellowish solution. This solution was then allowed to stand at room temperature for three hours. Excess oxalyl chloride and the solvent were removed under reduced pressure to get rid of excess oxalyl chloride. The remaining dark brown acid chloride solidified on cooling to a pale brown solid, m.p. 50-55°C. No attempt was, however, made to isolate this solid and purify it by crystallisation etc.. The acid chloride obtained was immediately used for condensation with the phenylethylamine (LXXII) as described below.

3-Benzyloxy-4-methoxy-N-2-(3-methoxy-4-benzyloxyphenyl)ethylacetamide (LXXIII).

To a well stirred mixture of 2-(3-methoxy-4-benzyloxyphenyl) ethyl amine (LXXII) (2.65 g.) dissolved in dry tetrahydrofuran (50-60 c.c.) and sodium hydroxide (0.55 g.) dissolved in water (2 c.c.) was added dropwise a solution of the 3-benzyloxy-4-methoxyphenylacetyl chloride (LXVIII) in dry tetrahydrofuran (30 c.c.). When all the acid chloride had been added (45 minutes), the reaction mixture was stirred for another 45 minutes, tetrahydrofuran removed under reduced pressure and the residue taken up in water (ca. 100 c.c.). The resulting mixture, adjusted to pH 10, was extracted with chloroform. The chloroform extract was washed successively with water, dilute hydrochloric acid (6N), aqueous sodium bicarbonate and water. The extract, dried as usual, left on evaporation a brownish solid (5.2 g.). Crystallisation of this crude solid from ethylacetate afforded clusters of very fine needles of 3-benzyloxy-4-methoxy-N-2-(3-methoxy-4-benzyloxy phenyl)-ethylacetamide (LXXIII) (3.95 g.), m.p. 138-9°C. (60% yield, calculated on the basis of the phenylacetic acid). $\nu_{max.}$ 3270, 1640 and 1545 cm^{-1} (bonded 'trans' secondary amide) and 1264, 1230 cm^{-1} (aromatic ethers) (Nujol).

	C	H	N
Found	74.84	6.31	2.88
$C_{32}H_{33}O_5N$ requires	75.12	6.50	2.74

1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydro isoquinoline hydrochloride (LXXIV).

A mixture of 3-benzyloxy-4-methoxy-N-2-(3-methoxy-4-benzyloxyphenyl)-ethylacetamide (LXXIII) (5 g.), dry toluene (80 c.c.) and freshly distilled phosphorus oxychloride (1.5 c.c.) was heated in a bath, maintained at a temperature of 115-120° for forty five minutes. The solvent and excess phosphorusoxychloride were removed, under reduced pressure, on a steam bath. While the solvent etc., were being removed, a brownish solid separated and caused considerable bumping. At this stage an excess dry light petroleum (60-80) was added and the supernatant clear liquid decanted off. The remaining brownish solid was washed several times with dry petroleum and the petroleum was finally driven off by warming under reduced pressure on a steam bath. The dry brown solid was crystallised from ethanol using a little charcoal at the same time when 1-(3-benzyloxy-4-methoxy benzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline hydrochloride

(LXXIV) (4.18 g.), was obtained. Rhombic plates, m.p. 198-200°C.(dec.). [80% yield, calculated on the basis of the phenylethylacetamide (LXXIII)].

	C	H	N	Cl
Found	72.30	5.80	3.03	6.85
$C_{32}H_{31}O_4N.HCl$ requires	72.49	6.08	2.64	6.69

1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline methiodide. (LXXV).

1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline hydrochloride (LXXIV) (1 g.) suspended in excess ether was shaken vigorously with aqueous sodium bicarbonate. The aqueous phase was again extracted with ether several times as rapidly as possible. The remaining aqueous phase turned pink on standing. The ether extracts, dried over anhydrous potassium carbonate, were evaporated at low temperatures under reduced pressure. The resulting 'free' base tended to turn pinkish on exposure to atmosphere and was immediately used for methiodide formation.

The 'free' base, obtained above, was dissolved in dry benzene (20 c.c.), the solution flushed with oxygen free nitrogen (10 minutes), methyliodide (1 c.c.) added, the whole mixture stoppered

while nitrogen was still passing and the stoppered flask was allowed to stand at room temperature for twenty four hours. The deposited methiodide was collected on a buchner funnel, washed with a little dry ether and recrystallised from methanol, m.p. 196-98° (0.76 g.). However, when the methiodide was recrystallised a third time to prepare an analytical sample, a dark brown gum resulted which failed to crystallise again. The methiodide was presumably labile and no attempt was made in later experiments to purify it by further crystallisation. This methiodide was therefore immediately used for borohydride reduction, as described below.

1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-2-methyl-1:2:3:4-tetrahydroisoquinoline. (LXXVI).

1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline hydrochloride (LXXIV) (4 g.) was converted into the methiodide (LXXV) as described above. The resulting methiodide (3.43 g.) (72% yield calculated on the basis of the dihydroisoquinoline hydrochloride), m.p. 196-98°C, was immediately suspended in 'AnalaR' methanol (150 c.c.) under nitrogen and sodium borohydride (3.5 g.) added slowly while the methiodide suspension was well stirred. When all the borohydride had been added (1 hour), stirring was continued

for half an hour and the reaction mixture allowed to stand overnight. Methanol was removed from the resulting solution under reduced pressure, the residue taken up in 2% aqueous sodium hydroxide (100 c.c.) and the milky mixture was extracted with ether. The ether extracts gave, on evaporation, an almost colourless oil (2.35 g.) which crystallised from benzene/light petroleum (60-80) to furnish colourless, long needles, m.p. 89°C (2 g., 52% yield, calculated on the basis of the dihydroisoquinoline hydrochloride).

	C	H	N
Found	78.10	6.91	3.09
$C_{33}H_{35}O_4N$ requires	77.77	6.92	2.75

It also formed a picrate in methanolic solution and recrystallised from the same solvent. Yellow, glistening plates, m.p. 149.5°C.

	C	H	N
Found	63.70	5.02	7.77
$C_{39}H_{38}O_{11}N_4$ requires	63.40	5.18	7.58

1-(3-Benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-3:4-dihydroisoquinoline methiodide (LXXV) was reduced to (LXXVI) by the

relatively cheaper potassium borohydride in equally good yields.

Attempted Hydrogenolysis of 1-(3-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-2-methyl-1:2:3:4-tetrahydroisoquinoline (LXVll) to laudanosoline-4':6-dimethyl ether. (LXVlll).

While the hydrogenolysis of 4-benzyloxy-3-methoxyphenylethyl amine (LXXll) to 4-hydroxy-3-methoxyphenylethylamine using palladised charcoal (10%) in ethanol containing a few drops of concentrated hydrochloric acid went smoothly, all attempts to hydrogenolyse (LXXVl) to (LXXVll) were unsuccessful. The variations tried consisted in employing a) palladised charcoal (10%) in ethanol containing four drops of hydrochloric acid, b) palladised barium sulphate (1%) in 'AnalaR' methanol containing two drops concentrated hydrochloric acid, c) palladised barium sulphate (10%) in methanol, freshly redistilled over calcium oxide, d) neat palladium generated 'in situ' by hydrogenating palladium chloride solution in methanol, e) palladised barium sulphate (10%) in acetic acid 'AnalaR' saturated with dry hydrochloric acid gas. Experiments using different batches of catalyst were also unsuccessful in hydrogenolysing the benzyloxy groups present in 1-(3-benzyloxy-4-methoxybenzyloxy)-6-methoxy-7-

benzyloxy-2-methyl-1:2:3:4-tetrahydroisoquinoline.

Laudanosoline-4':6-dimethyl ether (LXVIII).

A solution of 1-(3-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-2-methyl-1:2:3:4-tetrahydroisoquinoline (LXXVI) (211 mgs.) in 3N acetic acid was slowly dropped into aqueous hydrochloric acid (25%) (20 c.c.) heated in a bath maintained at 130-135°C. The benzyl chloride formed in the reaction mixture was distilled away as soon as it was formed. When all the base solution had been added and the distillate obtained was no longer turbid, the reaction mixture was carefully evaporated to dryness, under reduced pressure, on a steam bath. The residue was evaporated repeatedly with ethanol. The remaining foam was made alkaline with aqueous sodium bicarbonate and the resulting free base immediately extracted with ether as usual. Removal of ether under reduced pressure and at a low temperature yielded a white amorphous material which failed to crystallise. It gave a violet colour with alcoholic ferric chloride. Attempts to prepare its oxalate, hydrobromide, perchlorate etc., were not successful.

However, a picrate could be prepared in methanolic solution although its separation was extremely slow and it could not be obtained in a nicely crystalline form even after repeated crystallisations from diverse solvents. The yield of laudanosoline-4':6-dimethyl ether isolated as the picrate varied from 40-55% calculated on the basis of (LXXVI).

The analytical sample of the picrate was prepared from acetone/alcohol and dried for two days at 50°C under vacuum.

	C	H	N
Found	53.50	4.79	10.07
$C_{25}H_{26}O_{11}N_4$ requires	53.75	4.69	10.03

Laudanosoline-4':6-dimethyl ether obtained above was also methylated.with diazomethane to yield a product whose picrate was found identical (mixed m.p.'s and I.R. spectra) with laudanosine picrate.

Paper Chromatography of Authentic Alkaloid Mixtures and Oxidation Mixtures.*

Paper: Whatman No.1 paper was used throughout except for the large scale resolution of the oxidation mixtures when Whatman '3MM' paper was used. However, it was found that untreated paper gave rise to unsatisfactory resolution and after a trial of several methods of treating the papers, namely, impregnation in $M/_2$ potassium chloride, treatment with buffers of McIlvain's standard, $M/_5$ disodium hydrogen phosphate etc., treatment with $M/_7$ potassium dihydrogen phosphate was found to give the best results. Use of a paper strip (about 40 cm. long) was desirable.

Technique: 'Descending technique' was used throughout except in a few preliminary experiments.

Solvent: Several solvent systems were tried, important being a) n-butanol-conc. HCl-distilled water (100:2:20) b) n-butanol-acetic acid 'AnalaR'-water (4:1:2) c) n-butanol-propionic acid-water (100:2:20) d) n-butanol-formic acid 'AnalaR'-water (100:2:20), e) ethyl acetate-acetic acid 'AnalaR'-water (100:20:20), f) amyl alcohol-formic acid 'AnalaR'-water (100:18:4), g) toluene-acetic acid-water (100:10:10 ml.).

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* The author thanks Dr. W.R. Rees for the facilities of equipment used in this work.

The organic solvents like butanol, amyl alcohol, etc., were freshly distilled before use. n-Butanol-'AnalaR' formic acid-water (100:2:20) was found to give most satisfactory results.

Spots: The materials used for spotting in the preliminary experiments consisted of laudanosine, corytuberine, methylated corytuberine, glaucine, boldine, etc.. 50-100 γ was found a satisfactory amount used on a single spot.

Reagent for Development: Although examination in ultra violet light was helpful in certain cases, the modified Dragendorff Reagent [40] was used throughout.

Procedure: The 'paper strips' of desired lengths (40-50 cm. long) of Whatman No.1 or 3MM were passed through a bath of $^{M}/_{7}$ potassium dihydrogen phosphate (aqueous) taking care that the strips do not wrinkle and only the terminal one or two inches of the strip are touched by hand. These are pressed between two big filter sheets and dried for about three days at room temperature.

The solvent system, i.e. n-butanol-'AnalaR' formic acid-water (100:2:20) was prepared a day before use.

The mixtures to be resolved were spotted with the help of a micro pipette (50-100 γ). The papers were then equilibrated for

24 hours with the solvent in well sealed tanks maintained at 24°C.. The remaining solvent was then run in and the irrigation continued overnight for about twelve hours. The 'paper strips' were then allowed to dry at room temperature (fume cupboard) for a day and sprayed with the modified Dragendorff reagent (fresh).

Attempted Oxidation of Laudanosoline-4':6-dimethyl ether (LXVIII) with potassium ferricyanide.

Laudanosoline-4':6-dimethyl ether (referred to as the 'phenol' in the sequel) was obtained fresh by the hydrolysis of 1-(3-benzyloxy-4-methoxybenzyl)-6-methoxy-7-benzyloxy-2-methyl-1:2:3:4-tetrahydroisoquinoline (LXVII) as described on page 193.

'Oxygen-free nitrogen' used to deaerate the various solutions has been previously passed through two wash-bottles containing Fieser's solution [44] and then into a wash bottle of saturated lead acetate solution and finally into a bottle containing distilled water.

Work up of Oxidation Reaction - General Procedure.

1) The reaction mixture, acidified with 6N. hydrochloric acid, was saturated with sodium chloride, pH adjusted to about 8 (with sodium bicarbonate) and thoroughly exhausted with chloroform. The chloroform extracts, washed and dried as usual, were evaporated at about 40°C under reduced pressure. The residue was split into phenolic and

non-phenolic portions in some early experiments but in each case the so called non-phenolic material consisted either of polymers (as shown by paper chromatography) or one which did not show any αβ-unsaturated carbonyl absorption in the infra red spectrum. Subsequently, the total bases from chloroform extracts were methylated with diazomethane (one week in the refrigerator). The methylated product was examined spectroscopically (ultra violet and infra red) and subjected to paper chromatography as already explained. In no case, however, the infra red showed any bands characteristic of αβ-unsaturated ketones.

ii) In the case of the oxidation experiments (C), involving two immiscible phases, the organic phase was separated at the end and the residue worked up as above. The aqueous phase was saturated with sodium chloride, pH adjusted to about 8 and the mixture was thoroughly exhausted with chloroform. However, the residue obtained after methylation in each case consisted of polymeric material only as shown by paper chromatography.

A. Experiments employing the 'Usnic Acid Technique'.

The alkali solution was thoroughly flushed with 'oxygen-free nitrogen', and the 'phenol' dissolved in deaerated alkali by gentle warming, if necessary. The solution was cooled to 0° and the aqueous

solution of potassium ferricyanide was added slowly under nitrogen (oxygen-free) with good stirring. The reaction mixture at the end was worked up in the usual way. The essential details of these experiments are summarised in Table I(p. 203)

B. Experiments employing the 'Simultaneous Addition Technique'.

The phenol and the oxidant were added slowly and simultaneously to the alkali, deaerated in the usual way and the reaction mixture was worked up as usual.

[For results of these experiments see Table II, p.204].

C. Experiments involving two immiscible phases.

A typical experiment illustrating the technique used here is described below. [For results of these experiments see Table III, p.205].

A mixture of 'AnalaR' sodium bicarbonate (8.266 g.) dissolved in freshly boiled distilled water and the phenol (570 mgs.) dissolved in 'AnalaR' ethyl acetate (2.5 l.) was thoroughly flushed with oxygen-free nitrogen ($1\frac{1}{2}$ hours). The mixture was cooled to 0° and potassium ferricyanide (1.40 g.) in water (250 c.c.) was added slowly under oxygen-free nitrogen during 90 minutes with good stirring. After a further 90 minutes stirring, the clear deep green ethyl acetate phase

was separated, washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated to dryness at low temperature (bath temperature 40-50°C) under reduced pressure. The residue R_1 (300 mgs.) was methylated with diazomethane in the usual way (one week in the refrigerator). The remaining aqueous phase, saturated with 'AnalaR' sodium chloride was also thoroughly extracted with chloroform (about 3 l.). These chloroform extracts, however, left a residue R_2 (50 mgs.) which was found, after methylation and paper chromatography, to consist mainly of polymeric material besides a little laudanosine. The aqueous phase was therefore rejected in subsequent experiments and only the residue R_1 was collected.

Paper chromatography of the residue R_1, after methylation, showed that it consisted of a little polymer which did not move much on paper, and two other spots of R_f values 0.52 (very faint) and 0.64 (sharp) as compared with the R_f values, 0.66, 0.54, 0.69 and 0.86 for laudanosine, glaucine, methylated corytuberine and the dibenzyl ether of laudanosoline-4':6-dimethyl ether.

The I.R. spectrum of the crude total methylated bases did not show any characteristic bands in the 1680 cm^{-1} region.

The U.V. spectrum of the crude methylated product did not show the typical aporphine peak in the 300 mμ region [$\lambda_{max.}^{EtOH}$ 285 mμ (ε 6600) and ε at 300 mμ 2200].

The above experiment was repeated thirteen times. The methylated product (15 mgs. per strip) was streaked on Whatman 3MM paper strips (19 x 50 cm.) impregnated with $^{M}/_{7}$ potassium dihydrogen phosphate as already described. The zones containing the material with R_f 0.52 were located with the help of control strips cut out of the main strips. The material was eluted out of these strips with ethanol. A brownish gum (130 mgs.) was obtained in this way and was rechromatographed to get a product (50 mgs.) which was free from laudanosine as found by paper chromatography. This product was, however, acidic, presumably due to the presence of some formic acid left from the solvent mixture used during paper chromatography. It was taken up in very dilute acid, extracted with ether to get rid of neutral or acidic material. The aqueous phase was then neutralised with sodium bicarbonate and extracted with ether to get only 10 mgs. of a yellow gum. The U.V. spectra of this material, authentic laudanosine and authentic methylated corytuberine are shown side by side, (page 202). It had an R_f value 0.52 as compared with

laudanosine (0.59), glaucine (0.50) and methylated corytuberine (0.64 and 0.81). $\nu_{max.}$ 2910, 1595, 1515, 1464, 1254, 1107, 1030 cm^{-1} (thin film). $\nu_{max.}$ 2910, 2840, 1530, 1460, 1214, 1115 cm^{-1} (CCl_4 solution).

Attempts to crystallise this gum or to convert it into some crystalline derivatives like picrate, hydrobromide, methiodide were not successful and further attempts to characterise this gum were frustrated by the tedious procedure to get the extremely poor yield of the material.

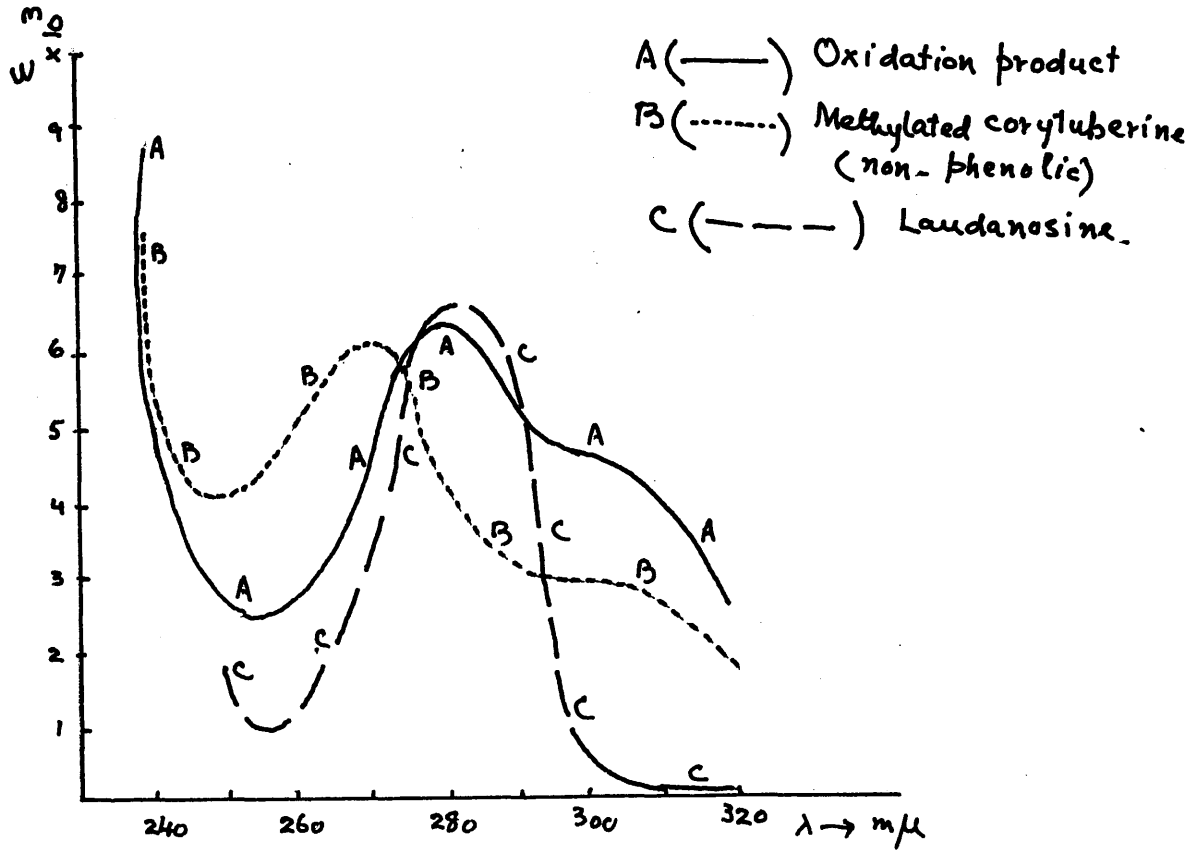

TABLE I (see page 206)

Experiment	Reactants[1] (ratio)	Dilution[2]	Reaction time (hours)	U.V.[3]	P.C.[4]
1	1:725:2.8	2	5	7000 4600	Polymer, 0.49(f), 0.61(s) [0.46, 0.60,-]
2	1:650:2.5	1.9	2	8800 5700	Polymer, 0.6(s) [0.50, 0.61,-]
3[a]	1:130:2.4	1.9	$2\frac{1}{4}$	8900 5500	0.18(s), 0.70(f) [0.59, 0.70, 0.75]
4	1:666:3	2	$\frac{1}{2}$	7600 5000	Polymer, 0.75(f) [0.6, 0.72, 0.81]
5	1:7.5:2.5	2	$\frac{1}{2}$	-	Polymer mainly

TABLE II (see page 204)

Experiment	Reactants[1] (ratio)	Dilution[2]	Reaction time (hours)	U.V.[3]	P.C.[4]
1	1:6.6:2.6	2.5	6	7500 4600	Trailing polymer, 0.73 [0.72, -, -]
2[b]	1:4.25:1	1.3	3	6000 1000	-
3[c]	1:142:2.5	1	6	7000 2000	Polymer (little), 0.72(s) [0.64,0.71,0.78]
4[c]	1:300:2.5	1.8	7	6500 2000	Polymer, 0.51(f), 0.62(s) [-, 0.63,-]
5[c]	1:145:11.2	2	6	No max. even at 280 mμ	Did not develop with the reagent at all.
6[c]	1:51:2.1	1.6	7	5200 2000	Trailing polymer, 0.58(f), 0.68(s) [0.56,0.67,-]
7[c]	1:51:2	2	3	6000 1500	Polymer, 0.7 [0.58, 0.71, 0.81].

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TABLE III (see page 206)

Experiment	Reactants[1] (ratio)	Organic[5] Solvent	Dilution[6]	Reaction time (hr.)	U.V.	P.C.
1	1:8.7:2.5	Ether (1.5)	1.5	2	5300 2000	Polymer (very little) 0.68(s) [-,0.7,-]
2[d]	1:23:2.4	Ether (1.5)	1.5	$3\frac{1}{4}$	6000 1800	Polymer (little) 0.53(f), 0.62(s) [0.54,0.64,0.71]
3[d,e]	1:51:2.5	Ethyl acetate (3)	3	3	6600 2200	Polymer (little) 0.51(f),0.64(s) [0.54,0.66,0.71]
4[f]	1:5.8:2.4	Benzene (2.8)	0.5	$\frac{1}{2}$	-	POLYMER (little) 0.6(f), 0.70(s) [0.58(f), 0.69,-]

Explanatory Notes for Tables I, II and II (see pages 203-205).

1. This column gives the molecular proportions of the reactants in the order: Phenol, Alkali and Oxidant. The Alkali used was sodium carbonate unless specified otherwise.

2. This column gives the total volume of water in litres for one millimole of the phenol oxidised.

3. Only the approximate values of ε at 280 and 300 mμ respectively are given. There was a distinct $\lambda_{max.}$ at about 280 mμ in each case unless otherwise specified. The corresponding values of ε for (6600, ~500) authentic laudanosine have not been given to avoid repetition.

4. P.C. stands for 'paper chromatographic data' and this column gives only the R_f values of 'spots' or 'smears' detected in the product after methylation. The R_f values of authentic glaucine, laudanosine and methylated corytuberine respectively, measured under similar conditions, are given in the square brackets immediately after the values of oxidation products. The words 'f' and 's' after the values stand for 'faint' or 'sharp and intense'.

5. It gives the total volume (litres) of the organic solvent used for every millimole of the phenol.

6. This column gives the volume (litres) of water used for one millimole of the phenol in the aqueous phase only.

a) Triethylamine was used here as the alkali.

b) About 70% of the starting phenol was recovered as laudanosine in a crystalline form (confirmed by mixed m.p. and derivatization).

c) Sodium hydroxide replaced sodium carbonate as alkali in these experiments.

d) Sodium bicarbonate was used in place of sodium carbonate.

e) See also the Experiment described in detail on page 199 .

f) Potassium hydroxide was the alkali used in this case. Here a benzene ('AnalaR') solution of the phenol was added under nitrogen to a mixture of alkaline ferricyanide (aqueous) and a large volume of benzene.

Extraction of Corytuberine from 'corydalis cava'.

300 g. of the air-dried roots of 'corydalis cava', finely ground, were soxhletted in methanol till the extract was colourless (about 18 hours). Methanol was removed under reduced pressure, 1 litre of hot water added to the residue and the mixture was adjusted to pH 3 with hydrochloric acid. The acidic mixture was then left in the refrigerator for forty eight hours. Some 'celite' filtered and was stirred into the mixture and filtered under suction through a thin layer of 'celite'. The residue in the funnel was washed with boiling water, acidified to pH 3 (500 c.c.). The combined filtrates were cooled in the refrigerator while the 'celite' mixed residue (R) was set aside.

The cooled aqueous filtrate was treated with a little charcoal in the cold, filtered and the filtrate exhausted thoroughly with chloroform (about 2.5 l.). The chloroform extract (C) was concentrated under reduced pressure to about 500 c.c. and clarified by filtration through a thin column of charcoal. The aqueous phase, after having been exhaustively extracted with chloroform, was filtrated and the filtrate (SC) was set aside.

The concentrated and clarified chloroform extract (C) was evaporated to dryness under reduced pressure and the residue dissolved in hot dilute hydrochloric acid (150 c.c.). The cooled solution (SR) was thoroughly exhausted with ether (about 2 l.). The remaining aqueous phase (ASR) was heated under reduced pressure to expel any dissolved ether. The cooled aqueous phase (ASR) was then made alkaline with excess potassium hydroxide solution. When the precipitate (BC) became granular on standing and trituration, it was filtered, washed with water and the filtrate (FC) thoroughly exhausted with ether (2 l.) (EC). The remaining aqueous phase (CES) was saturated with carbon dioxide, cooled thoroughly in the refrigerator and filtered. The precipitate (BCE) was set aside, while the aqueous filtrate was exhausted with ether (3 l.) (EEC). The remaining aqueous phase (CES_2) was set aside.

The acidic filtrate (SC) obtained above was neutralised with ammonia to pH 8, about 500 c.c. chloroform added and the mixture allowed to stand overnight. The alkaline mixture was thoroughly exhausted with chloroform (3 l.). The chloroform extract (AC) was concentrated under reduced pressure to about 1 l., filtered through a layer of charcoal to get rid of suspended impurities and

the filtrate then evaporated to dryness under reduced pressure. The residue was dissolved in hot dilute hydrochloric acid (50 c.c.). The solution on standing overnight had deposited some crystalline material but no attempt was made to separate them at this stage. The acidic mixture was made alkaline with potassium hydroxide and filtered. The precipitate (BS) was washed with water and the filtrate (FAC) exhausted with ether (2 l.) (ES). The remaining aqueous phase (AES) was saturated with carbon dioxide and the well cooled dark brown solution filtered. Filtration was extremely slow. The precipitate (BSE) was set aside, the filtrate exhausted with ether (3 l.) (EES). The remaining aqueous phase (AES_1) was set aside.

The precipitate (BSE) was digested with excess hot methanol and filtered. The residue obtained on evaporating off methanol could be crystallised from hot water to afford very fine dark brown needles which did not melt up to 290°, gave a cherry red colour with conc. nitric acid and had the typical ultra violet absorption spectrum of aporphines. But the yield so obtained was extremely small.

The aqueous phase (AES_1), in the meantime, deposited some

very fine needles after two to three days' standing. These crystals were washed successively with a little water, ethanol and ether, and dried overnight in a vacuum desiccator over sulphuric acid. The virtual insolubility of these crystals in most of the organic solvents like ether, chloroform, ethylacetate, acetone, etc., was reminiscent of the reported behaviour of corytuberine. However, they could be recrystallised from methanol and water. The recrystallised material had no definite melting point (Kofler block) except that some darkening of the crystals was observed around 225°C. An authentic specimen of corytuberine also exhibited similar behaviour on heating on the Kofler. Both the samples had identical I.R. and U.V. spectra. The two samples had also identical R_f values when run on paper (R_f values = 0.34). The identity of the two samples was further confirmed when the methiodides prepared from the two samples were also found identical by mixed melting point determination when no depression in the m.p. of 153-55°C. (dec.) was observed.

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